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# Pharmacologic and Nonpharmacologic Treatments for Major Depressive Disorder: Review of Systematic Reviews



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# Pharmacologic and Nonpharmacologic Treatments for Major Depressive Disorder: Review of Systematic Reviews

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## STRUCTURED ABSTRACT

**Objectives:** To summarize the evidence on more than 140 pharmacologic and nonpharmacologic treatment options for major depressive disorder (MDD) and to evaluate the confidence that patients and clinicians can have in the underlying science about their effects.

**Design:** Review of systematic reviews

**Data Sources:** MEDLINE®, Embase, Cochrane Library, PsycINFO, and Epistemonikos from 2011 up to February 2016 for systematic reviews of randomized controlled trials in adult patients with acute-phase MDD.

**Methods:** We dually reviewed abstracts and full-text articles, rated the risk of bias of eligible systematic reviews, and graded the strength of evidence.

**Results:** Fifteen systematic reviews provided data on 27 comparisons of interest. For general efficacy, only second-generation antidepressants were supported with high strength evidence, presenting small beneficial treatment effects but also a statistically significantly higher rate of discontinuation because of adverse events than patients on placebo (RR 1.88; 95% CI 1.0 to 3.28).

Only cognitive behavioral therapy is supported by reliable evidence (moderate strength of evidence) to produce responses to treatment similar to those of second-generation antidepressants (45.5% versus 44.2%; relative risk [RR], 1.10; 95% confidence interval [CI], 0.93 to 1.30). All remaining comparisons of nonpharmacologic treatments with second-generation antidepressants either led to inconclusive results or had substantial methodological shortcomings (low or insufficient strength of evidence).

**Conclusions:** The majority of nonpharmacologic interventions for treating MDD patients are not evidence-based. For patients with strong preferences against pharmacologic treatments,

clinicians should focus on therapies that have been compared directly with antidepressants.

**Systematic review registration:** International Prospective Register of Systematic Reviews (PROSPERO) registration number: 42016035580

## INTRODUCTION

According to World Health Organization (WHO) estimates, more than 350 million people worldwide suffer from depression, making it the second leading cause of disability throughout the world [1, 2]. Major depressive disorder (MDD) [3] is the most prevalent and disabling form of depression, affecting more than 30 million Europeans per year [4]. In the United States, the estimated lifetime prevalence of MDD is 16% [5]. In addition to its burden of disease, MDD exerts a negative impact on physical health [6-9] and adherence to medical treatment [10, 11].

Second-generation antidepressants (e.g., selective serotonin reuptake inhibitors [SSRIs] or selective serotonin norepinephrine reuptake inhibitors [SNRIs]) are the most commonly used treatments for acute MDD [12]. Most evidence-based guidelines recommend these medications as a first-step therapy [13, 14].

Nevertheless, patients with depression may prefer nonpharmacologic options because antidepressant therapies also come with considerable risks for harms. Up to 63% of patients on second-generation antidepressants experience adverse events; between 7% and 15% of patients discontinue treatment because of adverse events [15]. Concerns about the "addictiveness" of antidepressants are also a common reason for patients' skepticism about prescription medications [16, 17]; women and ethnic minorities, in particular, often prefer nonpharmacologic options as first-step treatments of depression [18, 19]. Antidepressants also have a substantially higher treatment-specific stigma than, for example, herbal remedies [20].

Such skepticism toward antidepressants reflects a general trend toward "natural treatments" throughout medicine. In 2012 an estimated 59 million persons in the United States spent 30.2 billion US$ in out-of-pocket expenses on some type of complementary health approach [21]. In a

survey of psychiatric patients, more than half of patients with self-reported depressive disorders used complementary and alternative medicine (CAM) therapies [22].

Nonpharmacologic treatment options for depression are vast. The Cochrane Depression and Neurosis Group lists 87 psychological interventions [23]; a comprehensive summary from an Australian patient advocacy group catalogued 56 CAM interventions for the treatment of depression (beyondblue: A guide to what works for depression [http://resources.beyondblue.org.au/prism/file?token=BL/0556]).

Because of the multitude of nonpharmacologic options, for clinicians the great challenge is how to balance patients' interest in alternatives to medications with the professional responsibility to choose treatments that are supported by scientific evidence.

The goal of this project was to provide an overview of the general efficacy and risk of harms of pharmacologic and nonpharmacologic interventions for treating patients with MDD. Furthermore, we strove to compare benefits and harms of nonpharmacologic interventions with second-generation antidepressants as the most common treatments for acute-phase MDD.

## METHODS

A review of systematic reviews is designed to compile evidence from multiple systematic reviews of interventions into one accessible, usable document [24]. We registered the protocol in PROSPERO (International Prospective Register of Systematic Reviews; registration number: 42016035580).

### Populations, Interventions, Comparators, Outcomes, Timing, and Settings

Table 1 presents the populations, interventions, comparators, outcomes, timing, and settings (PICOTS) criteria for eligibility of systematic reviews and meta-analyses. In this table, the term

"articles" refers to any systematic reviews or meta-analyses of randomized controlled trials (RCTs) published in peer-reviewed journals or other sources. We limited the publication period to 2011 or later because methods research indicates that more than 50% of systematic reviews are outdated 5.5 years after publication [25].

**Table1. Study eligibility criteria: Populations, interventions, comparators, outcomes, timing, and settings for the review of reviews**

| PICOTS | Specific Inclusion or Exclusion Criteria |
|---|---|
| **Population** | Adult (18+years) patients of all races and ethnicities with MDD who are **undergoing first-step treatment** during acute treatment phase.<br><br>We did ***not*** include populations with bipolar disorder, perinatal depression, dysthymia, seasonal affective disorder, or subsyndromal depression. We also did not include populations exclusively comprising patients with medical comorbidities and depression (e.g., populations with heart disease and depression or with cancer and depression) |
| **Interventions** | Eligible interventions had to be used **as an initial monotherapy** for acute-phase MDD<br><br><u>Psychological and behavioral interventions</u><br>• Behavior therapy/behavior modification<br>• Cognitive behavioral therapy<br>• Third wave cognitive behavioral therapies<br>• Psychodynamic therapies<br>• Humanistic therapies<br>• Integrative therapies<br>• Systemic therapies<br>• Other psychologically oriented interventions<br><u>Somatic treatments</u><br>• Any physical exercise<br>• Light therapy<br>• Tai Chi/Qigong<br>• Yoga<br><u>CAM therapies</u><br>• Dietary supplements (e.g., S-adenosyl-L-methionine [SAMe], omega-3 fatty acids)<br>• Herbal remedies (e.g., St. John's Wort, Chinese herbal formulations)<br>• Other CAM therapies used for the treatment of depression (e.g., acupuncture)<br><u>Pharmacologic interventions (for comparison with inactive interventions)</u><br>• Agomelatine<br>• Second-generation antidepressants<br>• Tricyclic antidepressants<br>• Off-label pharmacologic treatments<br><br>We did ***not*** include combination treatments |
| **Comparators** | • Any inactive intervention: (e.g., placebo, waiting list, sham acupuncture, no care)<br>• Second-generation antidepressants (bupropion, citalopram, desvenlafaxine, duloxetine, fluoxetine, escitalopram, fluvoxamine, levomilnacipran, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine, vilazodone, vortioxetine)<br><br>We did ***not*** include treatment as usual as a comparator because it is not standardized and cannot be considered an inactive intervention. |
| **Outcomes** | <u>Efficacy and effectiveness:</u> response, change of depression scores<br><u>Adverse events (safety and tolerability):</u> overall discontinuation, discontinuation because of adverse events, |
| **Timing** | No restrictions |

| | |
|---|---|
| **Setting** | All settings |
| **Time period** | Articles published in 2011 and later |
| **Study design** | Systematic reviews and meta-analyses (if based on a systematic review) of RCTs published in English, German, or Italian languages |

CAM, complementary and alternative medicine; MDD, major depressive disorder; RCT: randomized controlled trial.

For eligible psychological interventions, we used the Cochrane Depression and Neurosis Group classification [23]. For CAM we were interested in any intervention that the nonprofit patient advocacy group *beyondblue* listed as a "nonmedical" intervention for treating depressed patients [26]. Supplementary File 1 lists the 87 eligible psychological interventions and the 56 eligible CAM interventions.

## Literature Searches

To identify relevant systematic reviews or meta-analyses, we searched MEDLINE® (via PubMed), EMBASE, the Cochrane Library, PsycINFO, and Epistemonikos. We used both index terms (e.g., Medical Subject Headings, Emtree) and free-text key words to search for MDD. We limited the electronic searches to "human," "English, German, or Italian language," "adults," and systematic reviews or meta-analyses. We searched sources from 1 January 2011 to 23 February 2016.

We imported all citations into an electronic database (EndNote X.6.0.1). The search strategies and yields of the searches appear in Supplementary File 2.

## Screening Process

We developed and pilot-tested review forms using the eligibility criteria in Table 1. Two persons independently reviewed abstracts and full-text articles. We resolved discrepancies by consensus or by consulting a third, senior investigator. If more than one systematic review on the same intervention met eligibility criteria, we chose the most recent review with the lowest risk of

bias. For each eligible systematic review, we determined whether RCTs included in it also met our inclusion criteria (see Table 1).

**Data Abstraction**

We designed and used a structured form to ensure consistency of data abstraction. If all studies in a systematic review met our eligibility criteria, we extracted summary estimates from meta-analyses. If one or more studies did not meet our eligibility criteria, we extracted data from individual studies. For example, when systematic reviews included mixed populations with different depressive disorders, we retrieved individual publications on patients with MDD. When data were unclear or contradictory, we contacted review authors for clarification. A second senior reviewer evaluated the completeness and accuracy of the data abstraction.

**Risk of Bias Assessment**

To assess methodological limitations (risk of bias) of eligible systematic reviews, we used the AMSTAR (Assessing Methodological quality of Systematic Reviews) tool [27]. Two independent reviewers assigned ratings for study limitations. They resolved any disagreements by consensus or by consulting a third, independent party. For the risk of bias of individual studies in a systematic review, we relied on the ratings of the original reviews' authors.

**Evidence Synthesis**

Our aim was to depict the magnitude of beneficial and harmful treatment effects and the confidence that patients and clinicians can have in the underlying science about these effects. We used effect estimates of systematic reviews if all included RCTs met our eligibility criteria. In instances where individual RCTs of eligible systematic reviews did not meet our eligibility

criteria (e.g., because they used treatment as usual as a control group), we recalculated quantitative analyses removing ineligible studies.

For general efficacy, we were interested in the improvement of depressive symptoms. We present standardized mean differences because methods of assessments differed substantially across systematic reviews. A standardized mean difference of 0 indicates that both groups had similar improvements; effects of -0.5 or -1 indicate that 69 or 84 percent of patients in the intervention group, respectively, had greater reductions on depression scores than the average patient in the control group. For the risk of harms, we present overall discontinuation rates and discontinuation rates because of adverse events.

For the comparative efficacy of nonpharmacologic treatments with second-generation antidepressants, we used relative risks (RR) of response to treatment (as defined by the authors but most commonly presented as a 50% reduction of symptoms on a depression rating scale). If necessary, we recalculated RR so that a value below 1 would represent fewer responses of patients using nonpharmacologic treatments and a value greater than 1 more responses. We present treatment effects also as absolute risk reductions or increases (differences in numbers of patients who respond to treatment, per 1000 treated patients) with the related 95% confidence intervals.

**Quantitative Analyses**

To summarize data quantitatively, we followed established guidance [28]. For all analyses, we used both random- and fixed-effects models. We report results of random-effects analyses (DerSimonian & Laird). In general, the findings from the random- and fixed-effects analyses were similar. We assessed statistical heterogeneity between studies by calculating the chi-squared statistic and Cochran's q. We used the $I^2$ statistic (the proportion of variation in study

estimates attributable to heterogeneity) to estimate the magnitude of heterogeneity. We examined potential sources of heterogeneity using sensitivity analyses and assessed publication bias with funnel plots and Kendall's tests.

For general efficacy, we estimated standardized mean differences using Hedges' g [29]. If systematic reviews presented effect sizes as Cohen's d, we used a correction factor (J) to convert to Hedges' g: ($J = 1 - \frac{3}{4df-1}$), where df stands for "degrees of freedom".

If systematic reviews presented effect estimates of general efficacy as dichotomous outcomes, we calculated log odds ratios and converted them first to Cohen's d ($d =$ LogOddsRatio x $\frac{\sqrt{3}}{\pi}$) and then to Hedges' g using the correction factor presented above. For each estimate we calculated variances and confidence intervals.

For all statistical calculations we used Microsoft Excel (version 2010, Microsoft, Redmond, Washington, USA) or Review Manager 5.3 (Version 5.3. Copenhagen, The Cochrane Collaboration, 2014).

**Strength of the Evidence**

We graded the strength of evidence based on guidance for AHRQ Evidence-based Practice Centers on the use of GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group [30, 31]. Strength of evidence can take four grades: high, moderate, low, or insufficient. We considered grades of high or moderate strength as reliable evidence.

**RESULTS**

Searches detected 2,042citations; 15 systematic reviews met our eligibility criteria and provided the most recent summaries of evidence on 27 comparisons of interest.[32-46] Eighteen additional systematic reviews formally met eligibility criteria, but their content was superseded

by at least one the 15 reviews mentioned above (Supplementary File 3). Figure 1 presents the flow of the literature; Table 2 presents characteristics of included reviews.

[Figure 1 about here]

For the majority of nonpharmacologic treatments, we did not find any systematically appraised evidence (Supplementary File 4). Figure 2 depicts the available comparisons of interest and the number of RCTs for each comparison.

[Figure 2 about here]

In the following sections, we first provide an overview of treatment effects of nonpharmacologic and common pharmacologic treatments compared with inactive interventions.

We then present results on the comparative benefits and harms of nonpharmacologic interventions and second-generation antidepressants.

**Table 2: Characteristics of included systematic reviews**

| Review | Risk of Bias | Years Covered by Searches | Eligible Study Designs | Population | Intervention | Control | K Relevant Studies, N Analyzed |
|---|---|---|---|---|---|---|---|
| Abbass 2014 [42] | Low | NR to July 2012 | RCTs | Adults, ≥18 years of age, with common mental disorders, allowed comorbid medical or psychiatric disorders (relevant study of African American women, 20-50 years of age, with depression) | Psychodynamic therapies (short term) | Inactive treatment (wait list) | Reduction: K=1, N=20 |
| Appleton 2015 [34] | Low | All years to May 2015 (except CINAHL, to September 2013) | RCTs, cross-over and cluster RCTs | Adults, ≥18 years of age, with a primary diagnosis of MDD or unipolar depressive disorder, allowed comorbid conditions | Omega-3 fatty acids (n-3PUFAs) | Inactive treatment (pill-placebo) | Reduction: K=6, N=308<br>Discontinuation (overall): K=7, N=446 |
| Cujipers 2014 [43] | Medium | 1966 to January 2012 | RCTs | Adults diagnosed with a depressive disorder, allowed comorbid medical or psychiatric disorders | Humanistic therapy (Supportive therapy) | Inactive treatment (pill-placebo) | Reduction: K=1, N=101 |
| | | | | | Integrative therapy (Interpersonal therapy) | Inactive treatment (pill-placebo) | Reduction: K=1, N=33 |
| Ekers, 2014 [41] | High | 1966 to January 2013 | RCTs | Adults, ≥16 years of age, with a primary diagnosis of depression | Third Wave CBT (Behavioral activation therapy) | Inactive treatment (waitlist, placebo) | Reduction: K=9, N=338 |
| Gartlehner 2015 [46] | Medium | January 1990 to September 2015 | RCTs, allowed nonrandomized studies for harms | Adults, ≥19 years of age, with MDD during initial treatment attempt or second treatment attempt among those who did not achieve remission after treatment with an SGA | Acupuncture | SGA | Response: K=93 (NWMA), N=173 |
| | | | | | CBT | SGA | Response: K=5 , N=660 |
| | | | | | Exercise | SGA | Response: K=90 (NWMA), N=0 |
| | | | | | Integrative therapy (Interpersonal psychotherapy) | SGA | Response: K=1, N=318 |
| | | | | | Omega-3 fatty acids | SGA | Response: K=92 (NWMA), N=40 |
| | | | | | SAMe | SGA | Response: K=90 |

| Review | Risk of Bias | Years Covered by Searches | Eligible Study Designs | Population | Intervention | Control | K Relevant Studies, N Analyzed |
|---|---|---|---|---|---|---|---|
| | | | | | | | (NWMA), N=0 |
| | | | | | St. John's wort | SGA | Response: K=9, N=1517 |
| | | | | | Third Wave CBT (Behavioral activation) | SGA | Response: K=2, N=243 |
| | | | | | SGA | Inactive treatment (pill-placebo) | Reduction: K=62, N=13759 |
| Josefsson 2014 [38] | High | NR to April 2012 | RCTs | Adults, ≥18 years of age, with depression or depressive symptoms | Exercise (aerobic or nonaerobic exercise, as monotherapy or with usual care, excluding eastern meditative practices) | Inactive treatment (no treatment, placebo) | Reduction: K=11, N=368 |
| Jun 2014 [33] | Medium | NR to February 2014 | RCTs, quasi-RCTs | Individuals of any age and either sex with depression, allowed comorbid diseases | Gan Mai Da Zao (decoction or modified decoction) | SGA | Response: K=3, N=148 |
| Linde 2015 [36] | Medium | NR to December 2013 | RCTs | Adults with prevalent or incident unipolar depressive disorder | St. John's wort | Inactive treatment (pill-placebo) | Reduction: K=4, N=619 |
| | | | | | | | Discontinuation (overall): K=4, N=619 |
| | | | | | | | Discontinuation (adverse events): K=3, N=522 |
| | | | | | TCA | Inactive treatment (pill-placebo) | Discontinuation (overall): K=4, N=484 |
| | | | | | | | Discontinuation (adverse events): K=3, N=421 |
| | | | | | SGA | Inactive treatment (pill-placebo) | Discontinuation (overall): K=5, N=1195 |
| | | | | | | | Discontinuation (adverse events): K=6, N=1572 |
| Liu 2015 [39] | High | NR to February 2014 | RCTs | Older adults, mean age ≥60 years, with depressive symptoms, and allowed comorbidities | Tai Chi, Qigong | Inactive treatment (newspaper reading or reading and discussion group, health education) | Reduction: K=3, N=193 |

| Review | Risk of Bias | Years Covered by Searches | Eligible Study Designs | Population | Intervention | Control | K Relevant Studies, N Analyzed |
|---|---|---|---|---|---|---|---|
| Okumura, 2014 [40] | High | 1994 to June 2013 | RCTs, cluster RCTs, quasi-RCTs | Adults, ≥18 years of age, with depression (elevated depressive symptoms, depressive disorders, or minor depression), allowed comorbid physical illness | CBT (group CBT, mindfulness-based cognitive therapy) | Inactive treatment (wait list, pill-placebo) | Reduction: K=8, N=787<br>Discontinuation (overall): K=7, N=834 |
| Sorbero 2015 [35] | Medium | NR to January 2015 | RCTs | Adults, ≥18 years of age, with a clinical diagnosis of MDD at enrollment or formerly depressed if primary outcome of study was depression relapse or recurrence | Acupuncture (specific, needle or electroacupuncture) | Inactive treatment (nonspecific acupuncture) | Reduction: K=3, N=168 |
| Taylor 2014 [45] | Medium | NR to March 2013 | RCTs | Adults with depression | Agomelatine | Inactive treatment (pill-placebo) | Reduction: K=12, N=3855 |
| Undurraga 2012 [37] | High | 1980 to August 2011 | RCTs | Adults in an acute, apparently unipolar MDD episode or with ≤10% identified cases of bipolar depression or diagnoses other than MDD | TCA | Inactive treatment (pill-placebo) | Reduction: K=21, N=3094 |
| Van Marwijk 2012 [44] | Low | All years to February 2012 | RCTs | Adults, ≥18 years of age, with a primary diagnosis of MDD, a depressive episode, or if considered depressed and eligible for antidepressant treatment by a clinician | Alprazolam | Inactive treatment (pill-placebo) | Reduction: K=5, N=603 |
| Yeung 2014 [32] | Medium | NR to May 2013 | RCTs, quasi-RCTs | Individuals diagnosed with | Chinese herbal medicine | SGA | Response: K=5, N=1360 |

| Review | Risk of Bias | Years Covered by Searches | Eligible Study Designs | Population | Intervention | Control | K Relevant Studies, N Analyzed |
|---|---|---|---|---|---|---|---|
| | | | | depression | | Inactive treatment (pill-placebo) | Reduction: K=2, N=171 |
| | | | | | Saffron | SGA | Response: K=1, N=38 |
| | | | | | | Inactive treatment (pill-placebo) | Reduction: K=2, N=80 |
| | | | | | | | Discontinuation (overall): K=2, N=80 |

CBT = cognitive behavioral therapy. K = number of studies that were eligible for review of reviews. N = number of participants in eligible studies. n-3PUFAs = n-3 polyunsaturated fatty acids. MDD = major depressive disorder. NR = not reported. RCT = randomized control trial. SGA = second-generation antidepressant. TCA = tricyclic antidepressants.

**Nonpharmacologic and pharmacologic treatments compared with inactive interventions**

*Benefits of treatments*

Fifteen systematic reviews provided data on 16 comparisons with inactive interventions (placebo, sham interventions, or waiting list) [32-34, 36-45, 47, 48]. Figure 3 provides an overview of treatment effects of nonpharmacologic and common pharmacologic treatments for MDD when compared with inactive interventions using standardized mean differences. The four commonly used pharmacologic interventions in the figure are agomelatine, alprazolam, second-generation antidepressants, and tricyclic antidepressants.

The comparisons in the figure are ordered by the strength of evidence grades and then alphabetically by the name of the intervention. Figure 3 also presents the numbers of trials and the total number of subjects in those trials; thus, the size of the circles reflects the numbers of participants (on a logarithmic scale). Supplementary File 5 provides detailed strength of evidence ratings.

[Figure 3 about here]

The only treatments for acute-phase MDD with high strength of evidence were second-generation antidepressants (Figure 3). Within this class, the medications rendered modest treatment effects (-0.35; 95% CI -0.31 to -0.38). Although the dataset included 24 unpublished studies [46], treatment effects might still be inflated because several methods studies indicate that publication bias is a serious problem in this drug class [49, 50].

Reviews on some psychological interventions (cognitive behavioral therapy [CBT], third wave CBT [focused more on developing skills and behaviors to improve quality of life than the first two generations of CBT], and psychodynamic therapies) reported large treatment effects (CBT: -0.80; 95% CI -0.49 to -1.12; third wave CBT: -0.97; 95% CI -0.6 to -1.34; psychodynamic therapies: -2.02; 95% CI -0.9 to -3.14; Figure 3). Studies of these three

psychological interventions used waiting lists as control interventions. Patients on waiting lists usually do not experience beneficial placebo effects, which can lead to artificially large treatment effects when active interventions are compared with waiting list controls. Placebo effects in psychiatric populations can be substantial; for example, on average 30% (range 12% to 52%) of patients in double-blinded trials of antidepressants achieved a treatment response (usually defined as a 50% reduction of symptoms) to placebo treatment [51].

For many of the therapies in Figure 3, the types of inactive comparators varied and involved different magnitudes of placebo effects. Consequently, comparisons of treatment effects across different interventions have to be made cautiously.

*Risk of harms*

Information on overall discontinuation and discontinuation because of adverse events was scarce. Figure 4 depicts the absolute risk reductions or increases for overall discontinuation and discontinuation because of adverse events – namely, the bars showing the 95% confidence intervals of either fewer or more discontinuations per 1000 patients. Only patients on second-generation antidepressants had a statistically significantly higher rate of discontinuation because of adverse events than patients on placebo (4.5% vs. 2.6%; RR 1.88, 95% CI 1.07 to 3.28). Most comparisons were of low or insufficient strength of evidence, indicating little certainty in the available effect estimates (details in Supplementary File 5).

[Figure 4 about here]

**Nonpharmacologic treatments compared with second-generation antidepressants**

Three systematic reviews provided data on response to treatment for 11 nonpharmacologic interventions (4 psychological, 6 CAM, and exercise) compared with second-generation antidepressants for the treatment of acute-phase MDD [32, 33, 46]. We used *response to*

*treatment* as defined by authors of the reviews; in most cases, this was a 50% reduction of symptoms as measured on a depression rating scale (e.g., Hamilton Depression Rating Scale). Figure 5 depicts the absolute risk reductions or increases for response to treatment per 1000 patients. As in the other figures, the comparisons are ordered by the strength of evidence grades and then alphabetically by the name of the intervention. These estimates are based on meta-analyses or, if meta-analyses were not feasible, on results from the largest and most reliable trial. Supplementary File 5 provides detailed information on our ratings of strength of evidence domains.

[Figure 5 about here]

*Psychological interventions*

One systematic review reported on the efficacy of four psychological treatments relative to second-generation antidepressants (Figure 5); these included CBT, integrative therapies, psychodynamic therapies, and third wave CBT [46]. The most reliable evidence (moderate strength of evidence) compared CBT with second-generation antidepressants. A meta-analysis of five RCTs of low or medium risk of bias with 660 patients provided consistent evidence that the two options had similar efficacy (45.5% versus 44.2%; RR, 1.10; 95% CI, 0.93 to 1.30) [52]. Including three high-risk-of -ias studies yielded similar results (RR, 0.98; 95% CI, 0.80 to 1.20) [52].

Integrative therapies also had response rates similar to those for antidepressants (low strength of evidence) [46]. Patients treated with third wave CBT had significantly higher response rates than those on antidepressants, but the strength of evidence was insufficient because of the small sample size and under-dosing of antidepressants in the available trial. No

evidence on response was available for psychodynamic therapies, but the available evidence indicated remission rates similar to those for second-generation antidepressants. [46]

*Complementary and alternative medicine interventions*

Three systematic reviews reported on comparisons with second-generation antidepressants for seven (of 56 eligible) CAM interventions – namely, acupuncture, Chinese herbal medicine (without Gan Mai Da Zao), Gan Mai Da Zao, omega-3-fatty acids, S-adenosyl-L-methionine (SAMe), St. John's wort, and saffron (Figure 5) [32, 33, 46]. Except for omega-3-fatty acids, none of the comparisons yielded statistically significant differences. Based on results of a network meta-analysis, patients using omega-3-fatty acids were statistically significantly less likely to achieve response than patients on antidepressants (RR 0.51; 95% CI 0.33 to 0.79) [46]. The reliability of results involving CAM interventions, however, is low. Therefore, the lack of statistical significance of most comparisons should not be interpreted as equivalence of treatment effects.

Some comparisons had wide confidence intervals (e.g., acupuncture, Gan Mai Da Zao, SAMe, saffron) rendering inconclusive findings about the comparative efficacy of treatments. Other comparisons had more precise results (e.g., Chinese herbal medicine or St. John's wort) but severe methodological shortcomings. For example, several trials of St. John's wort used moderate- or low-dose second-generation antidepressant regimens as comparators, not fully using the approved range of antidepressant doses [46]. Two of five trials comparing Chinese herbal medicine with antidepressants had serious design or analytic limitations such as flawed randomization or lack of allocation concealment [32].

*Exercise*

A network meta-analysis produced inconclusive results about differences in response rates between physical exercise and second-generation antidepressants (Figure 5) [46].

*Comparative harms*

The risks of adverse events and discontinuation of treatment because of adverse events were generally lower for patients treated with nonpharmacological interventions than for those receiving second-generation antidepressants, although differences did not always reach statistical significance. Patients on St. John's wort had a statistically significantly lower rate of discontinuation because of adverse events (3.8% vs. 6.8%; RR 0.59; 95% CI 0.38 to 0.89) [46]. Patients on any psychological treatment had a numerically lower risk for discontinuation of treatment because of adverse events (2.1% vs. 7.1%.; RR 0.37; 95% CI 0.12 to 1.12) [46]. Likewise, patients who used physical exercise discontinued treatment because of adverse events less often than those treated with antidepressants (0%. vs. 6%; RR 0.15; 95% CI 0.01 to 2.86), but the difference did not reach statistical significance [46]. Little evidence on adverse events or treatment discontinuation was available for most CAM interventions, particularly for Chinese herbal medicine or saffron [32, 33].

## DISCUSSION

Out of more than 140 interventions of interest, our review identified only 5 treatments for which the general efficacy for acute-phase MDD is supported by reliable evidence (i.e., evidence graded as high or moderate strength of evidence). Among those, CBT is the only psychological and St. John's wort the only CAM intervention. For the vast majority of nonpharmacological interventions, either no systematic review evidence was available or the certainty of the evidence was severely limited. When compared with second-generation antidepressants, only CBT had

similar efficacy based on moderate strength evidence. Overall, our analyses highlighted a lack of robust evidence for the majority of nonpharmacologic treatments.

To our knowledge, our study was the first review of systematic reviews assessing more than 140 interventions for treating adults with MDD. It provides a unique synthesis of the available, systematically appraised evidence on these treatment options, beyond the individual reviews on depression therapies that have been published over the past decade.

Our study does have several limitations, however. *First*, like any review of systematic reviews, we relied on results from other investigators or authors. Although most of the reviews had few problems in methods, conceivably these authors did miss some RCTs. Conceivably, RCTs are available for some interventions that have never been assessed systematically in a review. Therefore, the absence of systematic reviews cannot be equated with an absence of RCTs.

*Second*, we relied on the risk-of-bias appraisals of RCTs that authors of included systematic reviews had done. Most reviews used two independent reviewers to rate risk of bias; double checking their ratings was beyond the scope of our study. *Third*, reporting of characteristics of populations, interventions, comparators, and outcomes in included systematic reviews was often suboptimal. Frequently, we could not tell with certainty whether included populations were exclusively adult patients with acute-phase MDD; sometimes we could not determine the exact control interventions that authors had combined in their meta-analyses. We did not take several meta-analyses into consideration that combined studies with inactive treatments and treatment as usual as control interventions. Because treatment as usual cannot be viewed as "inactive," we believe that such meta-analyses will lead to biased results. *Fourth*, as in any literature review, the reliability of our results is directly related to the quality of the included studies. The strength of

evidence grades reflect the certainty of our results; for most cases, these grades were low or insufficient. Such low strength of evidence indicates that future studies might have a substantial impact on the effect estimates reported in our review. *Finally*, we did not take combination or augmentation strategies of antidepressants with nonpharmacologic interventions into consideration, but in clinical practice this is a common treatment strategy.

We believe that our results have important clinical implications. They provide patients and clinicians with solid and up-to-date information about which treatment options have (or have not) been evaluated in rigorous systematic reviews. For patients with strong preferences against pharmacologic treatment, clinicians can offer therapies that have been compared directly with antidepressants. CBT, for example, is a well-supported, first-step alternative to pharmacologic treatment of MDD. Other psychologic or CAM interventions might be equally effective, or nearly so, but the evidence base is less reliable. The majority of psychologic and CAM interventions, however, are not evidence-based; given better alternatives, clinicians should probably advise against them. Such shared and informed decisionmaking might enhance treatment adherence and improve treatment outcomes for patients with MDD. This is especially important because treatment continuity is one of the main challenges in treating such patients [53].

Our findings also highlight key areas of future research needs. Subsequent trials need to address gaps in our current knowledge about the comparative benefits and harms of pharmacologic and nonpharmacologic treatments for MDD. In particular, major research gaps pertain to information about the comparative risk of harms and patient-relevant outcomes such as functional capacity and quality of life. For patients and clinicians alike, balancing benefits and harms based on objective information is crucial. Lack of information about harms can lead to a

biased knowledge base and the potential for decisions that cause more harm than good. Future studies should assess benefits and harms with standardized measures to allow for more direct comparisons across studies.

In the end, even in the absence of clearly informative evidence, clinicians and patients need to make decisions. They can discuss what is known and what is not known about the available options to treat MDD, and our work provides a way to start those conversations. For patients with strong preferences against pharmacologic treatments, clinicians should focus on therapies that have been compared directly with antidepressants. This review provides a framework to guide discussion of the potential options.

## DECLARATIONS

**Ethics approval:** Not required

**Consent for publication:** Not required

**Availability of data and materials:** The datasets used for meta-analyses are available from the corresponding author on reasonable request.

**Competing interests:** All authors declare that they have no competing interests.

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**Authors' contributions:** Gerald Gartlehner, Kathleen Lohr, and Meera Viswanathan developed the concept of the study; Gerald Gartlehner, Judith Greimel, Gernot Wagner, Nina Matyas, and Viktoria Titscher conducted the literature review; Gernot Wagner, Nina Matyas, and Viktoria Titscher abstracted data and conducted statistical analyses; Meera Viswanathan and Linda Lux rated the risk of bias of included systematic reviews; Gerald Gartlehner, Gernot Wagner, and Nina Matyas graded the strength of evidence; Bradley Gaynes provided clinical expertise throughout the study; Gerald Gartlehner and Kathleen Lohr wrote the first draft of the manuscript; all authors reviewed the manuscript and provided comments and revisions.

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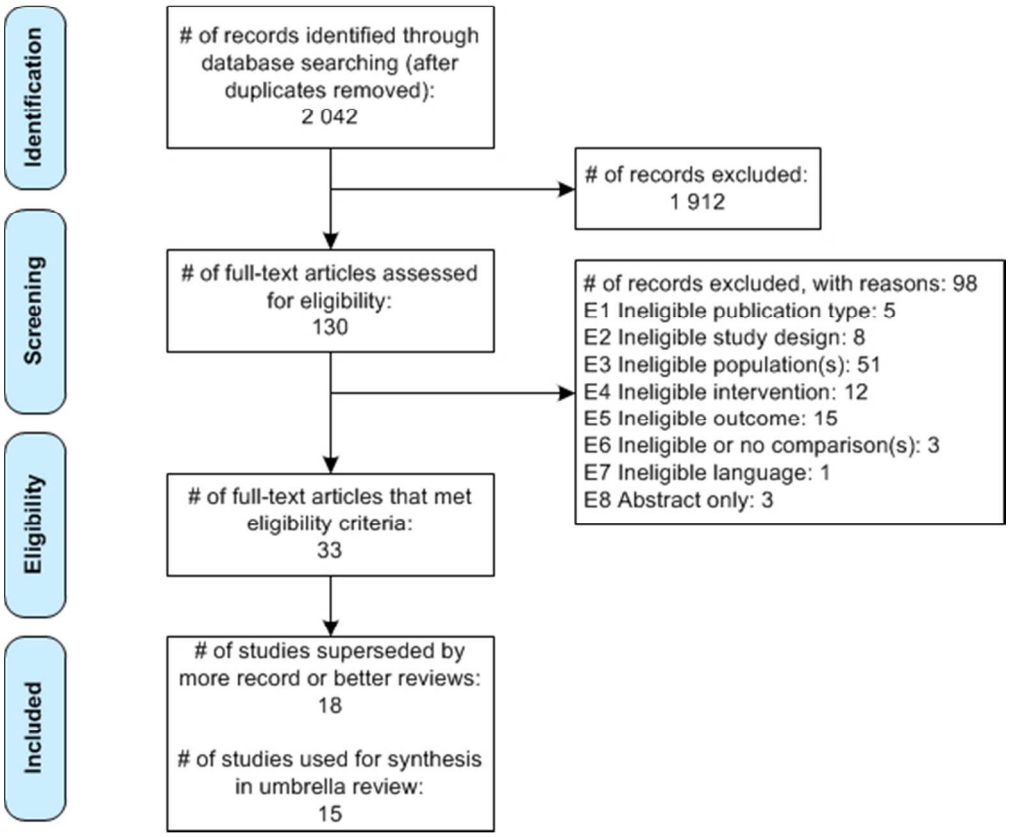
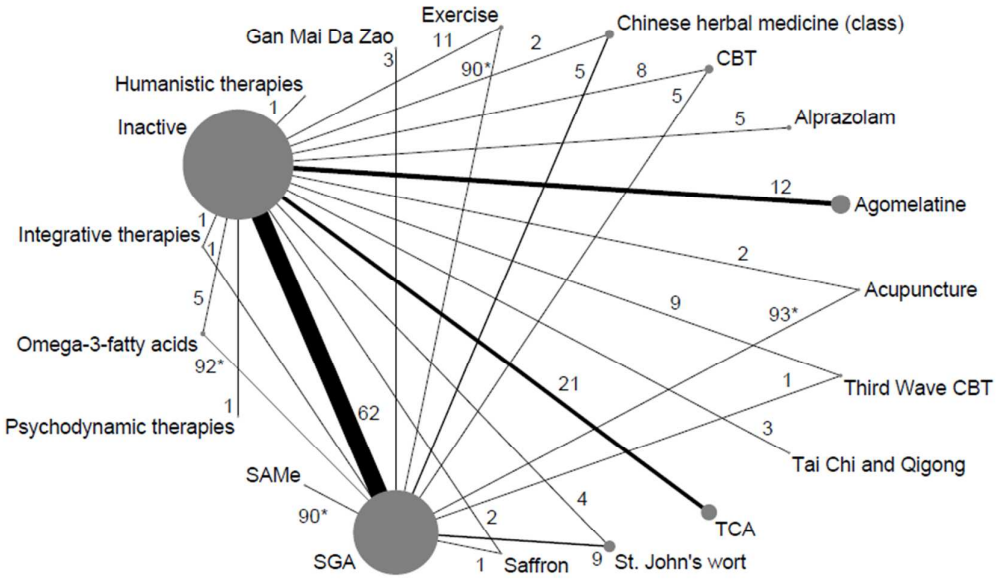
**Figure 1: PRISMA diagram for review of systematic reviews of treatments for major depressive disorder in adults**




155x144mm (96 x 96 DPI)

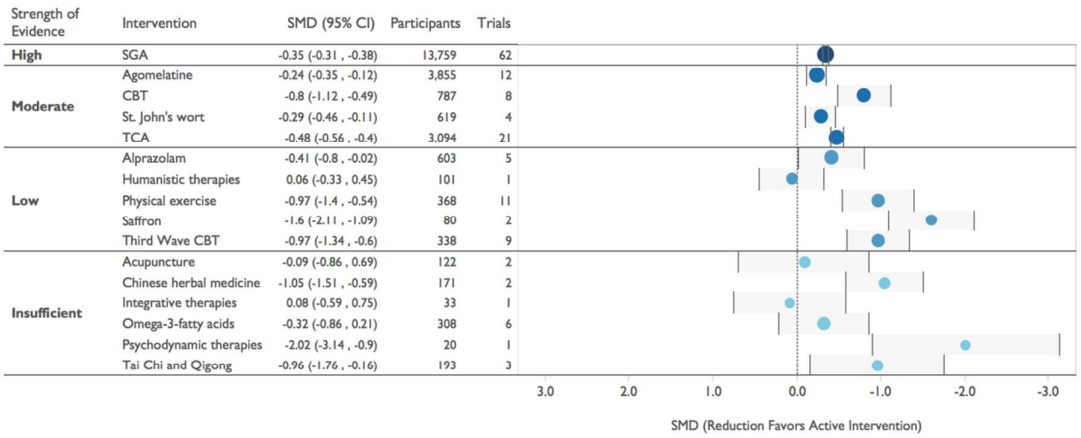
**Figure 2: Comparisons of nonpharmacologic and selected pharmacologic treatments for acute phase major depressive disorder in adults**




Abbreviations: CBT, cognitive behavioral therapy; SAMe, S-adenosyl-L-methionine; SGA, second-generation antidepressants; TCA, tricyclic antidepressants.

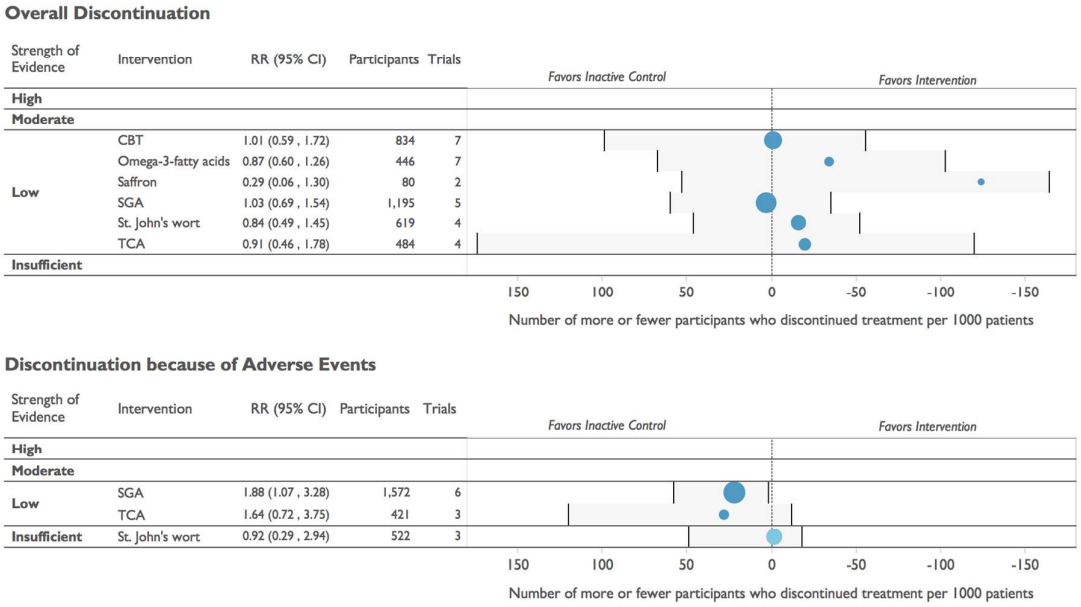
*Number of trials contributing to effect estimates in network meta-analyses

**Figure 3: Overview of the strength of evidence of nonpharmacologic and pharmacologic interventions compared with inactive interventions for the treatment of adult major depressive disorder**



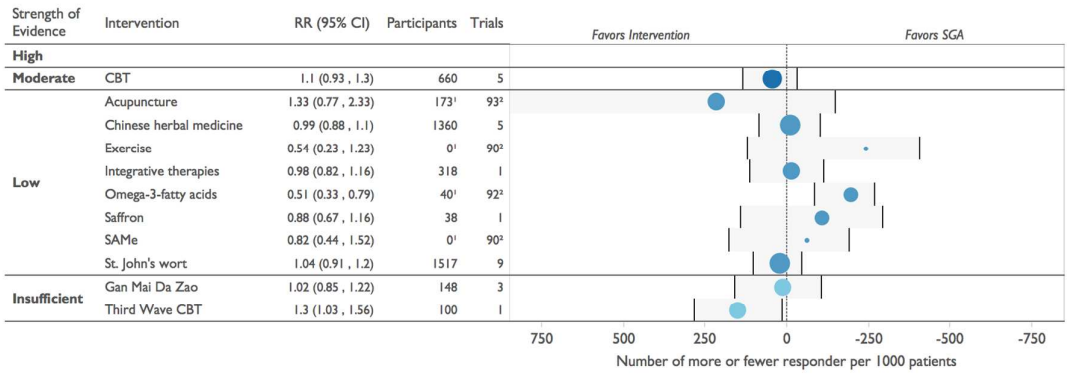

Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval; SGA, second-generation antidepressants; SMD, standardized mean difference; TCA, tricyclic antidepressants

**Figure 4: Absolute risk reductions or increases of overall discontinuation or discontinuation because of adverse events comparing nonpharmacologic interventions with inactive interventions**




Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval; SGA, second-generation antidepressants; TCA, tricyclic antidepressants

**Figure 5: Absolute risk reductions or increases of response to treatment comparing nonpharmacologic interventions with second-generation antidepressants for the treatment of adult major depressive disorder**




Abbreviations: CBT, cognitive behavioral therapy; ;CI, confidence interval; NWMA, network meta-analysis; RR, relative risk; SAMe, S-adenosyl-L-methionine; SGA, second-generation antidepressants.

[1]Number of participants in trials that directly compared intervention with second-generation antidepressants.

[2] Number of trials in network meta-analysis that contributed to the effect estimate

**Supplementary File 1: Psychological and behavioral therapies**

| | |
|---|---|
| **Behavior Therapy / Behavior Modification**<br>• Activity Scheduling<br>• Assertiveness Training<br>• Aversion Therapy<br>• Behavior Contracting<br>• Behavior Modification<br>• Biofeedback, Psychology<br>• Contingency Management<br>• Conversion Therapy<br>• Distraction Therapy<br>• Exposure Therapy<br>• Pleasant Events<br>• Psychoeducation<br>• Problem-Focused<br>• Reciprocal Inhibition Therapy<br>• Relaxation Techniques<br>• Response Cost<br>• Sleep Phase Chronotherapy<br>• Social Skills Training | **Cognitive Behavioral Therapy**<br>• Problem Solving<br>• Rational Emotive Therapy<br>• Reality Therapy<br>• Restructuring<br>• Role Play<br>• Schemas<br>• Self-Control<br>• Stress Management |
| **Psychodynamic Therapies**<br>• Brief Psychotherapy<br>• Countertransference<br>• Freudian<br>• Group Therapy<br>• Insight Oriented Therapy<br>• Jungian<br>• Kleinian<br>• Object Relations<br>• Person Centered Therapy, Client-Centered Therapy<br>• Psychoanalytic Therapy<br>• Short-Term Psychotherapy<br>• Transference | **Third Wave Cognitive Behavioral Therapies**<br>• Acceptance And Commitment Therapy (ACT)<br>• Behavioral Activation<br>• Cognitive Behavioral Analysis System Of Psychotherapy (CBASP)<br>• Compassion-Focused<br>• Dialectical Behavior Therapy<br>• Diffusion<br>• Functional Analytic Psychotherapy (FAP)<br>• Metacognitive Therapy<br>• Mind Training<br>• Mindfulness |
| **Humanistic Therapies**<br>• Existential Therapy<br>• Experiential Therapy<br>• Expressive Therapy<br>• Griefwork<br>• Rogerian<br>• Non-Directive Therapy<br>• Supportive Therapy<br>• Transactional Analysis | **Integrative Therapies**<br>• Cognitive Analytical Therapy<br>• Counselling<br>• Eclectic Therapy<br>• Interpersonal Therapy<br>• Multimodal<br>• Transtheoretical |
| **Systemic Therapies**<br>• Conjoint Therapy<br>• Integrative Behavioral Couple Therapy (IBCT)<br>• Narrative Therapy<br>• Personal Construct<br>• Socioenvironmental Therapy<br>• Solution Focused Brief Therapy | **Other Psychologically-Oriented Interventions**<br>• Acting Out<br>• Age Regression Therapy<br>• Art Therapy<br>• Bibliotherapy<br>• Catharsis<br>• Colour Therapy<br>• Crisis Intervention<br>• Dance Therapy<br>• Drama Therapy<br>• Emotional Freedom Techniques<br>• Hypnotherapy<br>• Meditation [1]<br>• Morita Therapy<br>• Music Therapy<br>• Play Therapy<br>• Primal Therapy<br>• Psychodrama<br>• Reminiscence Therapy<br>• Sex Therapy |

Source: CCDAN [1]

**Supplementary File 1: Complementary and alternative medicine interventions**

| **Dietary Supplements** | **Other CAM Therapies** |
|---|---|
| • 5-hydroxy-L-tryptophan<br>• Carnitine/Acetyl-l-carnitine<br>• Chromium<br>• Folate<br>• Glutamine<br>• Inositol<br>• Magnesium<br>• Omega-3-fatty acids (fish oil)<br>• Phenylalanine<br>• SAMe (s-adenosylmethionine)<br>• Selenium<br>• Tyrosine<br>• Vitamin B6<br>• Vitamin B12<br>• Vitamin D<br>• Zinc | • Acupuncture<br>• Aromatherapy<br>• Autogenic training<br>• Ayurveda<br>• Bach Flower Remedies<br>• Bibliotherapy<br>• Craniosacral therapy<br>• Distraction<br>• Dolphins (swimming with)<br>• Homeopathyl<br>• Humor/humor therapy<br>• Hydrotherapy<br>• LeShan distance healing<br>• Massage<br>• Meditation<br>• Melatonin<br>• Music<br>• Nature-assisted therapy<br>• Negative air ionisation<br>• Painkillers<br>• Pets<br>• Prayer<br>• Qigong<br>• Recreational dancing<br>• Reiki<br>• Relaxation training<br>• Sleep deprivation<br>• Tai chi<br>• Yoga<br>• Young tissue extract |
| **Herbal Remedies** | |
| • Borage<br>• Ginkgo biloba<br>• Kampo<br>• Lavender<br>• Marijuana<br>• Rhodiola rosea (golden root)<br>• Saffron<br>• Schizandra<br>• St John´s wort<br>• Traditional Chinese herbal medicine | |

Source: beyondblue: A guide to what works for depression [http://resources.beyondblue.org.au/prism/file?token=BL/0556

1. **CCDAN Topic List: Intervention - Psychological therapies** [http://ccdan.cochrane.org/sites/ccdan.cochrane.org/files/uploads/CCDAN%20topics%20list_psychological%20therapies%20for%20website.pdf]

**Supplementary File 2: Search Strategies of Report for the American Psychological Association and Updates Search, by Date**

**22 February 2016**

PsycINFO (via EBSCOhost):

| Search | Query | Limiters/Expanders | Results |
|---|---|---|---|
| S1 | DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" | Search modes - Find all my search terms | 101,801 |
| S2 | TI ( (major OR mild OR moderate OR severe OR Chronic OR subsyndromal OR minor) N1 depress* ) OR AB ( (major OR mild OR moderate OR severe OR Chronic OR subsyndromal OR minor) N1 depress* ) | Search modes - Find all my search terms | 41,285 |
| S3 | TI ( Dysthymic N1 (Disorder OR depress*) ) OR AB ( Dysthymic N1 (Disorder OR depress*) ) | Search modes - Find all my search terms | 1,121 |
| S4 | TI Dysthymia OR AB Dysthymia | Search modes - Find all my search terms | 2,176 |
| S5 | S1 OR S2 OR S3 OR S4 | Search modes - Find all my search terms | 113,379 |
| S6 | (DE "Treatment Outcomes" OR DE "Psychotherapeutic Outcomes") OR (DE "Treatment Effectiveness Evaluation") OR (DE "Treatment") | Search modes - Find all my search terms | 112,193 |
| S7 | DE "Drug Therapy" | Search modes - Find all my search terms | 120,211 |
| S8 | DE "Antidepressant Drugs" OR (DE "Dietary Supplements") | Search modes - Find all my search terms | 18,225 |
| S9 | TI ( therap* OR psychotherap* OR antidepress* OR exercise* OR treat* ) OR AB ( therap* OR psychotherap* OR antidepress* OR treat* OR exercise*) OR SU ( therap* OR psychotherap* OR antidepress* OR exercise* ) | Search modes - Find all my search terms | 892,909 |
| S10 | S6 OR S7 OR S8 OR S9 | Search modes - Find all my search terms | 906,948 |
| S11 | S5 AND S10 | Search modes - Find all my search terms | 58,713 |
| S12 | S11 AND (TX adult*) | Search modes - Find all my search terms | 36,836 |
| S13 | (ZC "meta analysis") or (ZC "systematic review") | Search modes - Find all my search terms | 25,727 |
| S14 | TI ( meta analy* OR metaanaly* OR systematic review ) OR AB ( meta analy* OR metaanaly* OR systematic review ) | Search modes - Boolean/Phrase | 36,119 |
| S15 | S13 OR S14 | Search modes - Find all my search terms | 39,677 |
| S16 | S12 AND S15 | Search modes - Find all my search terms | 699 |
| S17 | S12 AND S15 | Limiters - Publication Year: 2011-2016 | 438 |

Epistemonikos:

| Query | Results |
|---|---|
| ((title:("major depress*" OR Dysthym* OR "subsyndromal depress*" OR "chronic depress*" OR "minor depress*") OR abstract:("major depress*" OR Dysthym* OR "subsyndromal depress*" OR "chronic depress*" OR "minor depress*")) OR title:depression) AND (title:(treat* OR therap* OR antidepress* OR psychotherap*) OR abstract:(therap* OR antidepress* OR psychotherap*)) NOT (child* OR adolesc*) | 4063 |
| Publication Type: Systematic Review | 911 |
| Publication Year: 2011 - 2016 | 433 |

**23 February 2016**

MEDLINE (via PubMed):

| Search | Query | Results |
|---|---|---|
| #1 | Search Depressive Disorder[Mesh:NoExp] | 63391 |
| #2 | Search Depressive Disorder, Major[Mesh] | 21464 |
| #3 | Search Dysthymic Disorder[Mesh] | 1038 |
| #4 | Search Depression[Mesh] | 166475 |
| #5 | Search major depress* [tiab] | 35468 |
| #6 | Search mild depress* [tiab] OR moderate depress* [tiab] OR severe depress* [tiab] | 5759 |
| #7 | Search Dysthymic Disorder [tiab] OR Dysthymic depress*[tiab] | 647 |
| #8 | Search Dysthymia [tiab] | 1927 |
| #9 | Search Chronic depression [tiab] | 753 |
| #10 | Search subsyndromal depress* [tiab] | 191 |
| #11 | Search minor depress* [tiab] | 1116 |
| #12 | Search #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 | 178291 |
| #13 | Search therapy[sh] | 5857380 |
| #14 | Search Treatment Outcome[mh] | 732516 |
| #15 | Search therapeutic use[sh] | 3706139 |
| #16 | Search drug therapy[sh] | 1814651 |
| #17 | Search Antidepressive Agents[Mesh] | 49765 |
| #18 | Search Psychotherapy[Mesh] | 164737 |
| #19 | Search Therapeutics[Mesh:NoExp] | 8140 |
| #20 | Search Complementary Therapies[Mesh] OR Phototherapy[Mesh] OR Magnetic Field Therapy[Mesh] OR Physical Therapy Modalities[Mesh] OR Combined Modality Therapy[Mesh] OR Dietary Supplements[Mesh] OR Drug Therapy[Mesh] | 1575104 |
| #21 | Search Exercise[Mesh] | 134612 |
| #22 | Search cam [sb] | 1017418 |
| #23 | Search therapy [tiab] OR therapies [tiab] | 1621447 |
| #24 | Search treat* [tiab] | 4211222 |
| #25 | Search antidepress* [tiab] | 53976 |
| #26 | Search #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 | 9792757 |
| #27 | Search (#12 AND #26) | 107642 |
| #28 | Search (#27 AND systematic[sb]) | 4376 |
| #29 | Search "Animals"[Mesh] NOT "Humans"[Mesh] | 4179330 |
| #30 | Search (#28 NOT #29) | 4373 |
| #31 | Search "Age Groups"[Mesh] NOT "Adult"[Mesh] | 1618187 |
| #32 | Search (#30 NOT #31) | 4074 |
| #33 | Search (#32) AND ("2011"[Date - Publication] : "3000"[Date - Publication]) | 1984 |
| #34 | Search (#33 AND (eng[la] OR ger[la] OR ita[la])) | 1936 |

Cochrane Library:

| Search | Query | Results |
|---|---|---|
| #1 | [mh ^"Depressive Disorder"] | 5022 |
| #2 | [mh "Depressive Disorder, Major"] | 2882 |
| #3 | [mh "Dysthymic Disorder"] | 146 |
| #4 | [mh Depression] | 6454 |
| #5 | ((major or mild or moderate or severe or chronic or subsyndromal or minor) next depress*):ti,ab,kw | 8376 |
| #6 | (dysthymic next (disorder or depress*)):ti,ab,kw | 251 |
| #7 | dysthymia:ti,ab,kw | 463 |
| #8 | depression:ti | 12767 |
| #9 | {or #1-#8} | 23563 |
| #10 | [mh /TH,TU,DT] | 286797 |
| #11 | [mh "Treatment Outcome"] | 111009 |
| #12 | [mh "Antidepressive Agents"] | 5363 |
| #13 | [mh psychotherapy] | 18569 |
| #14 | [mh therapeutics] | 267124 |
| #15 | [mh exercise] | 16764 |
| #16 | *therap*:ti,ab | 236773 |
| #17 | treat*:ti,ab | 410566 |
| #18 | antidepress*:ti,ab | 8050 |
| #19 | {or #10-#18} | 646531 |
| #20 | #9 and #19 | 19387 |
| #21 | #20 Publication Year from 2011 | 2265 |
| #22 | #21 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations | 688 |

EMBASE:

| No. | Query | Results |
|---|---|---|
| #1 | 'depressive disorder*':ab,ti OR depress*:ti | 155336 |
| #2 | 'major depression'/exp | 44356 |
| #3 | 'dysthymia'/exp | 6867 |
| #4 | (major NEAR/2 depress*):ab,ti | 46183 |
| #5 | ((mild OR moderate OR severe) NEAR/2 depress*):ab,ti | 11586 |
| #6 | (dysthymic NEAR/2 (disorder OR depress*)):ab,ti | 914 |
| #7 | dysthymia:ab,ti | 2465 |
| #8 | ((chronic OR subsyndromal OR minor) NEAR/2 depress*):ab,ti | 5010 |
| #9 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 | 185651 |
| #10 | 'therapy'/de OR 'acupuncture'/exp | 1290300 |
| #11 | 'treatment outcome'/exp | 1105591 |
| #12 | 'drug therapy'/de | 410725 |
| #13 | 'antidepressant agent'/exp | 345376 |
| #14 | 'psychotherapy'/exp | 206641 |
| #15 | 'meditation'/exp | 4793 |
| #16 | 'alternative medicine'/exp | 39082 |
| #17 | 'physical medicine'/exp | 471331 |
| #18 | 'natural products and their synthetic derivatives'/de OR 'omega 3 fatty acid'/exp OR 's adenosylmethionine'/exp OR 'hypericum perforatum extract'/exp | 34035 |
| #19 | 'hypericum perforatum'/exp | 2683 |
| #20 | 'exercise'/exp | 249136 |
| #21 | therapy:ab,ti OR therapies:ab,ti | 2076954 |
| #22 | treat*:ti | 1458457 |
| #23 | antidepress*:ab,ti | 74142 |
| #24 | #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 | 5575205 |
| #25 | #9 AND #24 | 82902 |
| #26 | [cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim | 174779 |
| #27 | 'systematic review':ab,ti | 83779 |
| #28 | 'meta analy*':ab,ti OR metaanaly*:ab,ti | 113691 |
| #29 | #26 OR #27 OR #28 | 223713 |
| #30 | #25 AND #29 | 3737 |
| #31 | #30 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) | 3221 |
| #32 | 'animal'/exp NOT 'human'/exp | 4608503 |
| #33 | #31 NOT #32 | 3219 |
| #34 | 'groups by age'/exp NOT 'adult'/exp | 2250957 |
| #35 | #33 NOT #34 | 3110 |
| #36 | #35 AND [2011-2016]/py | 1399 |
| #37 | #36 AND ([english]/lim OR [german]/lim OR [italian]/lim) | 1353 |

**Supplementary File 3:** Eligible reviews that were superseded by other reviews (k=18)

| Superseded review | Intervention | Included review | Reason for decision |
|---|---|---|---|
| Amick et. al., 2015[1] | CBT | Gartlehner et. al., 2015[2] | AHRQ report provides more comprehensive data |
| Cuijpers et. al., 2011[3] | Integrative therapies | Cuijpers et. al., 2014[4] | Superseded by more recent review |
| Cuijpers et. al., 2012[5] | Humanistic therapies | Cuijpers et. al., 2014[4] | Superseded by more recent review |
| de Souza Moura et. al., 2015[6] | Exercise | Josefsson et. al., 2014[7] | Study considered more suitable |
| Gartlehner et. al., 2016[8] | Non-pharmacologic versus pharmacologic therapies | Gartlehner et. al., 2015[2] | AHRQ report provides more comprehensive data |
| Grosso et al., 2014[9] | Omega-3-fatty acids | Appleton et al., 2015[10] | Superseded by more recent review |
| Hausenblas et. al., 2013[11] | Saffron | Yeung et. al., 2014[12] | Superseded by more recent review |
| Hausenblas et. al., 2015[13] | Saffron | Yeung et. al., 2014[12] | Yeung used the same two studies for Saffron and provide additional data for Chinese herbal medicine |
| Johnsen et. al., 2015[14] | CBT | Okumura et. al., 2014[15] | Study considered more suitable |
| Kirkham et. al., 2015[16] | Integrative therapies | Cuijpers et. al., 2014[4] | Study considered more suitable |
| Linde et. al., 2015[17] | CBT | Okumura et. al., 2014[15] | Study considered more suitable |
| Linde et. al., 2015[18] | CBT | Okumura et. al., 2014[15] | Study considered more suitable |
| Nystrom et. al., 2015[19] | Exercise | Josefsson et. al., 2014[7] | Study considered more suitable |
| Ren et. al., 2015[20] | Chinese herbal medicine (class) | Yeung et. al., 2014[12] | Yeung provides more comprehensive data |
| Weitz et. al., 2015[21] | CBT | Gartlehner et. al., 2015[2] | Study considered more suitable |
| Yang et. al., 2015[22] | Omega-3-fatty acids | Appleton et. al., 2015[10] | Superseded by more recent review |
| Yin et. al., 2014[23] | Tai Chi and Qigong | Liu et. al., 2015[24] | Superseded by more recent review |
| Zhang et. al., 2014[25] | Shuganjieyu | Yeung et. al., 2014[12] | Yeung included studies for Shuganjieyu and provides additional data for Chinese herbal medicine |

CBT: Cognitive behavioural therapy

1. Amick HR, Gartlehner G, Gaynes BN, et al. Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: systematic review and meta-analysis. BMJ. 2015;351:h6019. doi: 10.1136/bmj.h6019. PMID: 26645251.
2. Gartlehner G, Gaynes BN, Amick HR, et al. Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder. Rockville MD: Rockville (MD): Agency for Healthcare Research and Quality (US); ; 2015.
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**Supplementary File 4:** Summary of the availability of evidence comparing nonpharmacologic interventions with inactive treatments and second-generation antidepressants

| Intervention | Comparison with Second- generation antidepressants | Comparison with Inactive Interventions | Intervention | Comparison with Second- generation Antidepressants | Comparison with Inactive Intervention |
|---|---|---|---|---|---|
| **Psychological Interventions (classes)** | | | | | |
| Cognitive behavioral therapy | Y | Y | Behavior Therapy or Behavior Modification | N | N |
| Third wave cognitive behavioral therapies | Y | Y | Systemic therapies | N | N |
| Integrative therapies | Y | Y | Other psychologically oriented interventions | N | N |
| Psychodynamic therapies | N | Y | | | |
| Humanistic therapies | N | Y | | | |
| **Complementary and Alternative Medicine (CAM) Interventions** | | | | | |
| *Dietary Supplements* | | | | | |
| Omega-3-fatty acids (fish oil) | Y | Y | Magnesium | N | N |
| SAMe (s-adenosylmethionine) | Y | N | Phenylalanine | N | N |
| 5-H-hydroxy-L-tryptophan | N | N | Selenium | N | N |
| Carnitine/Acetyl-l-carnitine | N | N | Tyrosine | N | N |
| Chromium | N | N | Vitamin B6 | N | N |
| Folate | N | N | Vitamin B12 | N | N |
| Glutamine | N | N | Vitamin D | N | N |
| Inositol | N | N | Zinc | N | N |
| *Herbal Remedies* | | | | | |
| Saffron | Y | Y | Kampo | N | N |
| St John´s Wort | Y | Y | Lavender | N | N |
| Traditional Chinese herbal medicine (class) | Y | Y | Marijuana | N | N |
| Gan Mai Da Zao | Y | N | Rhodiola rosea (golden root) | N | N |
| Borage | N | N | Schizandra | N | N |
| Ginkgo biloba | N | N | | | |
| *Other CAM Therapies* | | | | | |
| Acupuncture | Y | Y | Massage | N | N |
| Aromatherapy | N | N | Meditation | N | N |
| Autogenic Training | N | N | Music | N | N |
| Ayurveda | N | N | Nature-assisted therapy | N | N |
| Bach flower remedies | N | N | Painkillers | N | N |
| Bibliotherapy | N | N | Prayer | N | N |
| Craniosacral therapy | N | N | Recreational dancing | N | N |
| Distraction | N | N | Reiki | N | N |
| Dolphins (swimming with) | N | N | Relaxation training | N | N |
| Homeopathy | N | N | Sleep deprivation | N | N |
| Humor/humor therapy | N | N | Yoga | N | N |
| Hydrotherapy | N | N | Young tissue extract | N | N |
| LeShan distance healing | N | N | | | |
| **Somatic Treatments** | | | | | |
| Any physical exercise | Y | N | Light therapy | N | N |
| Tai Chi – Qi Gong | N | Y | | | |

Abbreviations: N, No available evidence; Y, evidence was available

**Supplementary File 5. Summary of findings regarding response (nonpharmacologic interventions compared to second-generation antidepressants for the treatment of adult major depressive disorder).**

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **CBT compared to SGA for MDD** [1] | | | | | | | | | | | | |
| 5 | randomized trials | not serious | not serious | not serious | serious [1] | none | 142/312 (45.5%) | 154/348 (44.3%) | **RR 1.10** (0.93 to 1.30) | **44 more per 1.000** (from 31 fewer to 133 more) | ⊕⊕⊕◯ MODERATE | 1. Few events |
| **Acupuncture compared to SGA for MDD** [1] | | | | | | | | | | | | |
| 93 [1] | randomized trials | not serious | not serious | serious [2] | serious [3] | none | 46/73 (63.0%) | 65/100 (65.0%) | **RR 1.33** (0.77 to 2.33) | **215 more per 1.000** (from 150 fewer to 865 more) | ⊕⊕◯◯ LOW | 1. Based on network meta-analysis; 2 studies provided direct comparisons<br>2. Results are based on network meta-analysis<br>3. Few events not meeting optimal information size |
| **Chinese herbal medicine compared to SGA for MDD** [2] | | | | | | | | | | | | |
| 5 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 594/707 (84.0%) | 558/653 (85.5%) | **RR 0.99** (0.88 to 1.10) | **9 fewer per 1.000** (from 85 more to 103 fewer) | ⊕⊕◯◯ LOW | 1. 4 out of 5 studies are rated high risk of bias<br>2. Few events; study does not meet optimal information size |
| **Exercise compared to SGA for MDD** [1] | | | | | | | | | | | | |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| 90 [1] | randomized trials | not serious | not serious | serious [2] | serious [3] | none | 31/100 (31.0%)[4] | 53/100 (53.0%)[4] | **RR 0.54** (0.23 to 1.23) | **244 fewer per 1,000** (from 122 more to 408 fewer) | ⨁⨁◯◯ LOW | 1. Based on network meta-analysis; No studies provided data for a direct comparison<br>2. Estimates are based on network meta-analysis.<br>3. Few events, confidence intervals cross threshold of appreciable difference.<br>4. No data from head-head studies available. Event rate is based on average events in placebo controlled trials |
| **Integrative therapies compared to SGA for MDD** [1] | | | | | | | | | | | | |
| 1 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 98/160 (61.3%) | 99/158 (62.7%) | **RR 0.98** (0.82 to 1.16) | **13 fewer per 1.000** (from 100 more to 113 fewer) | ⨁⨁◯◯ LOW | 1. High risk of bias due to insufficient reporting of methods and baseline differences between groups in duration of illness.<br>2. Sample size that does not fulfill optimal information size |
| **Omega-3 fatty acids compared to SGA for MDD** [1] | | | | | | | | | | | | |
| 92 [1] | randomized trials | serious [2] | not serious | serious [3] | not serious | none | 9/20 (45.0%) | 8/20 (40.0%) | **RR 0.51** (0.33 to 0.79) | **196 fewer per 1.000** (from 84 fewer to 268 fewer) | ⨁⨁◯◯ LOW | 1. Based on network meta-analysis; 2 studies provided direct comparisons<br>2. Suspected outcome reporting bias, only one of two studies reported response rates<br>3. Results are based on network meta-analysis |
| **Saffron compared to SGA for MDD** [2] | | | | | | | | | | | | |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 15/19 (78.9%) | 17/19 (89.5%) | **RR 0.88** (0.67 to 1.16) | **107 fewer per 1.000** (from 143 more to 295 fewer) | ⊕⊕◯◯ LOW | 1. Few events; study does not meet optimal information size |
| **SAMe compared to SGA for MDD** [1] | | | | | | | | | | | | |
| 90 [1] | randomized trials | not serious | not serious | serious [2] | serious [3] | none | 36/100 (36.0%)[4] | 53/100 (53.0%)[4] | **RR 0.82** (0.44 to 1.52) | **95 fewer per 1.000** (from 276 more to 297 fewer) | ⊕⊕◯◯ LOW | 1. Based on network meta-analysis; 0 studies provided direct comparisons<br>2. Results are based on network meta-analysis<br>3. Small study size<br>4. No data from head-head trials available. Event rate is based on average events in placebo controlled trials |
| **St. John's wort compared to SGA for MDD** [1] | | | | | | | | | | | | |
| 9 | randomized trials | not serious | serious [1] | serious [2] | not serious | none | 419/770 (54.4%) | 386/747 (51.7%) | **RR 1.04** (0.91 to 1.20) | **21 more per 1.000** (from 47 fewer to 103 more) | ⊕⊕◯◯ LOW | 1. Moderate heterogeneity (I2=47%)<br>2. Most studies compared to low or moderate dose SGA |
| **Gan Mai Da Zao compared to SGA for MDD** [3] | | | | | | | | | | | | |
| 3 | randomized trials | serious [1] | not serious | not serious | very serious [2] | none | 56/76 (73.7%) | 52/72 (72.2%) | **RR 1.02** (0.85 to 1.22) | **14 more per 1.000** (from 108 fewer to 159 more) | ⊕◯◯◯ VERY LOW | 1. No blinding of study participants and personnel<br>2. Studies do not meet optimal information size |
| **Third Wave CBT compared to SGA for MDD** [1] | | | | | | | | | | | | |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| 2 | randomized trial | very serious [1] | not serious | not serious | serious [2] | none | 66/93 (71.0%) | 76/150 (50.7%) | **RR 1.30** (1.03 to 1.56) | **152 more per 1.000** (from 15 more to 284 more) | ⊕◯◯◯ VERY LOW | 1. Dosage for one study capped below the upper limit of the typically prescribed range; suspected bias from one study's extremely high reported rates of response<br>2. Sample size does not fulfill optimal information size |

**CBT:** Cognitive behavioral therapy; **CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SGA:** Second generation antidepressant

**Supplementary File 4. Summary of findings regarding reduction in depression score (SMD) (nonpharmacologic and pharmacologic interventions compared to inactive interventions for the treatment of adult major depressive disorder).**

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **SGAs compared to inactive intervention for MDD** [1] | | | | | | | | | | | | |
| 62 | randomized trials | not serious | not serious | not serious | not serious | none | 8555 | 5204 | - | SMD **0.35 SD lower** (0.31 lower to 0.38 lower) | ⊕⊕⊕⊕ HIGH | |
| **Agomelatonin compared to inactive intervention for MDD** [4] | | | | | | | | | | | | |
| 12 | randomized trials | not serious | serious [1] | not serious | not serious | none | 2248 | 1607 | - | SMD **0.24 SD lower** (0.35 lower to 0.12 lower) | ⊕⊕⊕◯ MODERATE | 1. Some inconsistency, particularly between published and unpublished results; I-squared 66% |
| **CBT compared to inactive intervention for MDD** [5] | | | | | | | | | | | | |
| 8 | randomized trials | serious [1] | not serious | not serious | not serious | none | 378 | 409 | - | SMD **0.8 SD lower** (1.12 lower to 0.49 lower) | ⊕⊕⊕◯ MODERATE | 1. Outcomes assessors often not blinded |
| **St. John's wort compared to inactive intervention for MDD** [6] | | | | | | | | | | | | |
| 4 | randomized trials | not serious | not serious | not serious | serious [1] | none | 334 | 285 | - | SMD **0.29 SD lower** (0.46 lower to 0.11 lower) | ⊕⊕⊕◯ MODERATE | |
| **TCA compared to inactive intervention for MDD** [7] | | | | | | | | | | | | |
| 21 | randomized trials | not serious | not serious | not serious | not serious | publication bias strongly suspected [1] | 1577 | 1517 | - | SMD **0.48 SD lower** (0.56 lower to 0.4 lower) | ⊕⊕⊕◯ MODERATE | 1. Asymmetric funnel plot |
| **Alprazolam compared to inactive intervention for MDD** [8] | | | | | | | | | | | | |
| 5 | randomized trials | not serious | serious [1] | not serious | serious [2] | none | 305 | 298 | - | SMD **0.41 SD lower** (0.8 lower to 0.02 lower) | ⊕⊕◯◯ LOW | 1. I-squared 80%<br>2. Optimal information size not met |
| **Humanistic therapies compared to inactive intervention for MDD** [9] | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 51 | 50 | - | SMD **0.06 SD higher** (0.33 lower to 0.45 higher) | ⊕⊕◯◯ LOW | 1. Single study with 101 participants; does not meet optimal information size |
| **Physical exercise compared to inactive intervention for MDD** [10] | | | | | | | | | | | | |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| 11 | randomized trials | serious [1] | serious [2] | not serious | not serious | none | 189 | 179 | - | SMD **0.97 SD lower** (1.4 lower to 0.54 lower) | ⨁⨁◯◯ LOW | 1. Most studies did not blind outcomes assessors and did not use ITT analyses<br>2. Some confidence intervals do not overlap; I-squared not reported |
| **Saffron compared to inactive intervention for MDD** [2] | | | | | | | | | | | | |
| 2 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 40 | 40 | - | SMD **1.6 SD lower** (2.11 lower to 1.09 lower) | ⨁⨁◯◯ LOW | 1. Small studies; do not reach optimal information size |
| **Third Wave CBT compared to inactive intervention for MDD** [11] | | | | | | | | | | | | |
| 9 | randomized trials | serious [1] | serious [2] | not serious | not serious | none | 170 | 168 | - | SMD **0.97 SD lower** (1.34 lower to 0.6 lower) | ⨁⨁◯◯ LOW | 1. Most trials have limitations regarding methods of randomization and blinding of outcomes assessors<br>2. Some confidence intervals do not overlap |
| **Acupuncture compared to inactive intervention for MDD** [12] | | | | | | | | | | | | |
| 3 | randomized trials | serious [1] | serious [2] | not serious | very serious [3] | none | 86 | 82 | - | SMD **0.09 SD lower** (0.86 lower to 0.69 higher) | ⨁◯◯◯ VERY LOW | 1. One of the studies did not use ITT<br>2. I-squared high; some confidence intervals hardly overlap<br>3. Does not reach optimal information size |
| **Chinese herbal medicine compared to inactive intervention for MDD** [2] | | | | | | | | | | | | |
| 2 | randomized trials | very serious [1] | not serious | serious [2] | serious [3] | none | 113 | 58 | - | SMD **1.05 SD lower** (1.51 lower to 0.59 lower) | ⨁◯◯◯ VERY LOW | 1. High risk of bias in 1 out of 2 studies<br>2. Unclear how applicable studies are to Western populations<br>3. Does not fulfill optimal information size |
| **Integrative therapy compared to inactive intervention for MDD** [9] | | | | | | | | | | | | |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | randomized trials | serious [1] | not serious | not serious | very serious [2] | none | 19 | 14 | - | SMD **0.08 SD higher** (0.59 lower to 0.75 higher) | ⊕◯◯◯ VERY LOW | 1. Inadequate randomization and allocation concealment<br>2. Very few participants; does not meet optimal information size |
| **Omega-3 fatty acids compared to inactive intervention for MDD** [13] | | | | | | | | | | | | |
| 6 | randomized trials | serious [1] | serious [2] | not serious | serious [3] | none | 182 | 126 | - | SMD **0.32 SD lower** (0.86 lower to 0.21 higher) | ⊕◯◯◯ VERY LOW | 1. Some studies do not provide ITT results and strongly favor intervention; in most studies it is unclear how the taste of omega-3 fatty acids were masked<br>2. I-squared 77%; Some confidence intervals do not overlap<br>3. Confidence interval crosses clinically relevant benefits or harms |
| **Psychodynamic therapies compared to inactive intervention for MDD** [14] | | | | | | | | | | | | |
| 1 | randomized trials | serious [1] | not serious | not serious | very serious [2] | none | 10 | 10 | - | SMD **2.02 SD lower** (3.14 lower to 0.9 lower) | ⊕◯◯◯ VERY LOW | 1. Small study with unclear randomization and allocation concealment<br>2. Very small study; does not reach optimal information size |
| **Tai Chi and Qigong compared to inactive intervention for MDD** [15] | | | | | | | | | | | | |
| 3 | randomized trials | serious [1] | serious [2] | not serious | serious [3] | none | 91 | 102 | - | SMD **0.96 SD lower** (1.76 lower to 0.16 lower) | ⊕◯◯◯ VERY LOW | 1. Outcomes assessors not blinded in all trials<br>2. High I-squared; some confidence intervals not overlapping<br>3. Does not reach optimal information size |

**CBT:** Cognitive behavioral therapy; **CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SGA:** Second generation antidepressant; **SMD:** Standardized mean difference

**Supplementary File 4. Summary of findings regarding overall discontinuation (nonpharmacologic interventions compared to inactive interventions for the treatment of adult major depressive disorder).**

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **CBT compared to inactive intervention for MDD** [5] | | | | | | | | | | | | |
| 7 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 51/398 (12.8%) | 60/436 (13.8%) | **RR 1.01** (0.59 to 1.72) | **1 more per 1.000** (from 56 fewer to 99 more) | ⊕⊕◯◯ LOW | 1. Outcomes assessors often not blinded<br>2. Few events; confidence intervals cross clinically relevant benefits or harms |
| **Omega-3 fatty acids compared to inactive intervention for MDD** [13] | | | | | | | | | | | | |
| 7 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 61/272 (22.4%) | 45/174 (25.9%) | **RR 0.87** (0.60 to 1.26) | **34 fewer per 1.000** (from 67 more to 103 fewer) | ⊕⊕◯◯ LOW | 1. Some studies do not provide ITT results and strongly favor intervention; in most studies it is unclear how the taste of omega-3 fatty acids were masked<br>2. Confidence interval crosses clinically relevant benefits or harms |
| **Saffron compared to inactive intervention for MDD** [2] | | | | | | | | | | | | |
| 2 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 2/40 (5.0%) | 7/40 (17.5%) | **RR 0.29** (0.06 to 1.30) | **124 fewer per 1.000** (from 53 more to 164 fewer) | ⊕⊕◯◯ LOW | 1. Few events; study does not reach optimal information size |
| **SGAs compared to inactive intervention for MDD** [6] | | | | | | | | | | | | |
| 5 | randomized trials | not serious | not serious | not serious | serious [1] | publication bias strongly suspected [2] | 70/674 (10.4%) | 58/521 (11.1%) | **RR 1.03** (0.69 to 1.54) | **3 more per 1.000** (from 35 fewer to 60 more) | ⊕⊕◯◯ LOW | 1. Few events; does not meet optimal information size<br>2. Not all trials report overall discontinuation |
| **St. John's wort compared to inactive intervention for MDD** [6] | | | | | | | | | | | | |
| 4 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 26/334 (7.8%) | 29/285 (10.2%) | **RR 0.84** (0.49 to 1.45) | **16 fewer per 1.000** (from 46 more to 52 fewer) | ⊕⊕◯◯ LOW | 1. Very few events; optimal information size not reached |
| **TCA compared to inactive intervention for MDD** [6] | | | | | | | | | | | | |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| 4 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 50/246 (20.3%) | 53/238 (22.3%) | **RR 0.91** (0.46 to 1.78) | **20 fewer per 1.000** (from 120 fewer to 174 more) | ⊕⊕◯◯ LOW | 1. 3 out of 4 studies have serious limitations<br>2. Few events; does not meet optimal information size |

**CBT:** Cognitive behavioral therapy; **CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SGA:** Second generation antidepressant

**Supplementary File 4. Summary of findings regarding discontinuation due to adverse events (nonpharmacologic interventions compared to inactive interventions for the treatment of adult major depressive disorder).**

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **SGAs compared to inactive intervention for MDD** [6] | | | | | | | | | | | | |
| 6 | randomized trials | not serious | not serious | not serious | serious [1] | publication bias strongly suspected [2] | 41/865 (4.7%) | 18/707 (2.5%) | **RR 1.88** (1.07 to 3.28) | **22 more per 1.000** (from 2 more to 58 more) | ⊕⊕◯◯ LOW | 1. Few events; does not meet optimal information size<br>2. Not all trials report discontinuation because of adverse events |
| **St. John's wort compared to inactive intervention for MDD** [6] | | | | | | | | | | | | |
| 3 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 6/286 (2.1%) | 6/236 (2.5%) | **RR 0.92** (0.29 to 2.94) | **2 fewer per 1.000** (from 18 fewer to 49 more) | ⊕⊕◯◯ LOW | 1. Very few events; optimal information size not reached |
| **TCA compared to inactive intervention for MDD** [6] | | | | | | | | | | | | |
| 3 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 15/214 (7.0%) | 9/207 (4.3%) | **RR 1.64** (0.72 to 3.75) | **28 more per 1.000** (from 12 fewer to 120 more) | ⊕⊕◯◯ LOW | 1. 2 out of 3 studies have serious limitations<br>2. Few events; does not meet optimal information size |

**CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SGA:** Second generation antidepressant

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# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6-7 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supp File 2 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7-8 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 8 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8, Table 1 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 9 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 9-10 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 10 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 10 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 10, Figure 1, Supp File 3 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 11, Table 2 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 11, Supp File 4 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 12, Figures 2 - 5, Supp File 5 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 12-16 Figure 3 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 16-17 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 17 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 17-18 |
| **FUNDING** | | | |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 19 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

# Pharmacologic and Nonpharmacologic Treatments for Major Depressive Disorder: Review of Systematic Reviews



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# Pharmacologic and Nonpharmacologic Treatments for Major Depressive Disorder: Review of Systematic Reviews

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**Word count:** 3653

## STRUCTURED ABSTRACT

**Objectives:** To summarize the evidence on more than 140 pharmacologic and nonpharmacologic treatment options for major depressive disorder (MDD) and to evaluate the confidence that patients and clinicians can have in the underlying science about their effects.

**Design:** Review of systematic reviews

**Data Sources:** MEDLINE®, Embase, Cochrane Library, PsycINFO, and Epistemonikos from 2011 up to February 2017 for systematic reviews of randomized controlled trials in adult patients with acute-phase MDD.

**Methods:** We dually reviewed abstracts and full-text articles, rated the risk of bias of eligible systematic reviews, and graded the strength of evidence.

**Results:** Nineteen systematic reviews provided data on 28 comparisons of interest. For general efficacy, only second-generation antidepressants were supported with high strength evidence, presenting small beneficial treatment effects (standardized mean difference: -0.35; 95% confidence interval [CI] -0.31 to -0.38) but also a statistically significantly higher rate of discontinuation because of adverse events than patients on placebo (relative risk [RR]: 1.88; 95% CI 1.0 to 3.28).

Only cognitive behavioral therapy is supported by reliable evidence (moderate strength of evidence) to produce responses to treatment similar to those of second-generation antidepressants (45.5% versus 44.2%; RR: 1.10; 95% CI, 0.93 to 1.30). All remaining comparisons of nonpharmacologic treatments with second-generation antidepressants either led to inconclusive results or had substantial methodological shortcomings (low or insufficient strength of evidence).

**Conclusions:** In contrast to pharmacological treatments, the majority of nonpharmacologic interventions for treating MDD patients are not evidence-based. For patients with strong preferences against pharmacologic treatments, clinicians should focus on therapies that have been compared directly with antidepressants.

**Systematic review registration:** International Prospective Register of Systematic Reviews (PROSPERO) registration number: 42016035580

## ARTICLE SUMMARY

- This is the first review of systematic reviews assessing the benefits and harms of more than 140 pharmacologic and nonpharmacologic treatments for major depressive disorder.
- We used rigorous systematic review and novel graphical methods to summarize treatment effects and present the strength of the underlying evidence.
- Like any review of systematic reviews, we could draw conclusions only about interventions that had been assessed by systematic reviews.
- We did not take combination or augmentation strategies of antidepressants with nonpharmacologic interventions into consideration, but in clinical practice this is a common treatment strategy.

# INTRODUCTION

Major depressive disorder (MDD)[1] is the most prevalent and disabling form of depression, affecting more than 30 million Europeans per year.[2] In the United States, the estimated lifetime prevalence of MDD is 16%.[3] In addition to its burden of disease, MDD exerts a negative impact on physical health[4-7] and adherence to medical treatment.[8, 9]

Second-generation antidepressants (e.g., selective serotonin reuptake inhibitors [SSRIs] or selective serotonin norepinephrine reuptake inhibitors [SNRIs]) are the most commonly used treatments for acute MDD.[10] Most evidence-based guidelines recommend these medications as a first-step therapy.[11, 12]

Nevertheless, patients with depression may prefer nonpharmacologic options because antidepressant therapies also come with considerable risks for harms. Up to 63% of patients on second-generation antidepressants experience adverse events; between 7% and 15% of patients discontinue treatment because of adverse events.[13] Concerns about the "addictiveness" of antidepressants are also a common reason for patients' skepticism about prescription medications;[14, 15] women and ethnic minorities, in particular, often prefer nonpharmacologic options as first-step treatments of depression.[16, 17] Antidepressants also have a substantially higher treatment-specific stigma than, for example, herbal remedies.[18]

Such skepticism toward antidepressants reflects a general trend toward "natural treatments" throughout medicine. In 2012 an estimated 59 million persons in the United States spent 30.2 billion US$ in out-of-pocket expenses on some type of complementary health approach.[19] In a survey of psychiatric patients, more than half of patients with self-reported depressive disorders used complementary and alternative medicine (CAM) therapies.[20]

Nonpharmacologic treatment options for depression are vast. The Cochrane Depression and Neurosis Group lists 87 psychological interventions;[21] a comprehensive summary from an Australian patient advocacy group catalogued 56 CAM interventions for the treatment of depression (beyondblue: A guide to what works for depression [http://resources.beyondblue.org.au/prism/file?token=BL/0556]).

Because of the multitude of nonpharmacologic options, for clinicians the great challenge is how to balance patients' interest in alternatives to medications with the professional responsibility to choose treatments that are supported by scientific evidence.

The goal of this project was to provide an overview of the general efficacy and risk of harms of pharmacologic and nonpharmacologic interventions for treating patients with MDD. Furthermore, we strove to compare benefits and harms of nonpharmacologic interventions with second-generation antidepressants as the most common treatments for acute-phase MDD.

## METHODS

A review of systematic reviews is designed to compile evidence from multiple systematic reviews of interventions into one accessible, usable document.[22] We registered the protocol in PROSPERO (International Prospective Register of Systematic Reviews; registration number: 42016035580).

### Populations, Interventions, Comparators, Outcomes, Timing, and Settings

Table 1 presents eligibility criteria for populations, interventions, comparators, outcomes, timing, and settings of systematic reviews and meta-analyses. In this table, the term "articles" refers to any systematic reviews or meta-analyses of randomized controlled trials (RCTs) published in peer-reviewed journals or other sources. We limited the publication period to 2011

or later because methods research indicates that more than 50% of systematic reviews are outdated 5.5 years after publication.[23]

**Table 1. Study eligibility criteria: Populations, interventions, comparators, outcomes, timing, and settings for the review of reviews**

| PICOTS | Specific Inclusion or Exclusion Criteria |
|---|---|
| **Population** | Adult (18+years) patients of all races and ethnicities with MDD who are **undergoing first-step treatment** during acute treatment phase.<br><br>We did ***not*** include populations with bipolar disorder, perinatal depression, dysthymia, seasonal affective disorder, or subsyndromal depression. We also did not include populations exclusively comprising patients with medical comorbidities and depression (e.g., populations with heart disease and depression or with cancer and depression) |
| **Interventions** | Eligible interventions had to be used **as an initial monotherapy** for acute-phase MDD<br><br>Psychological and behavioral interventions<br>• Behavior therapy/behavior modification<br>• Cognitive behavioral therapy<br>• Third wave cognitive behavioral therapies<br>• Psychodynamic therapies<br>• Humanistic therapies<br>• Integrative therapies<br>• Systemic therapies<br>• Other psychologically oriented interventions<br>Somatic treatments<br>• Any physical exercise<br>• Light therapy<br>• Tai Chi/Qigong<br>• Yoga<br>CAM therapies<br>• Dietary supplements (e.g., S-adenosyl-L-methionine [SAMe], omega-3 fatty acids)<br>• Herbal remedies (e.g., St. John's Wort, Chinese herbal formulations)<br>• Other CAM therapies used for the treatment of depression (e.g., acupuncture)<br>Pharmacologic interventions<br>• Second-generation antidepressants<br>• Tricyclic antidepressants<br>• Off-label pharmacologic treatments<br><br>We did ***not*** include combination treatments |
| **Comparators** | • Any inactive intervention: (e.g., placebo, waiting list, sham acupuncture, no care)<br>• Second-generation antidepressants (agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, fluoxetine, escitalopram, fluvoxamine, levomilnacipran, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine, vilazodone, vortioxetine)<br><br>We did ***not*** include treatment as usual as a comparator because it is not standardized and cannot be considered an inactive intervention. |
| **Outcomes** | Efficacy and effectiveness: response, change of depression scores<br>Adverse events (safety and tolerability): overall discontinuation, discontinuation because of adverse events, |
| **Timing** | No restrictions |
| **Setting** | All settings |
| **Time period** | Articles published in 2011 and later |
| **Study design** | Systematic reviews* and meta-analyses (if based on a systematic review) of RCTs published in English, German, or Italian languages |

CAM, complementary and alternative medicine; MDD, major depressive disorder; RCT: randomized controlled trial.

* Systematic reviews are defined based on the Cochrane handbook as a literature review that attempts to collate all empirical evidence using a) clearly stated objectives and pre-defined eligibility criteria, b) an explicit reproducible methodology, c) a systematic search, d) an assessment of the validity of the findings of the included studies, and e) a systematic presentation, and synthesis, of the characteristics and findings of the included studies.[22]

For eligible psychological interventions, we used the Cochrane Depression and Neurosis Group classification.[21] For CAM we were interested in any intervention that the nonprofit patient advocacy group *beyondblue* listed as a "nonmedical" intervention for treating depressed patients.[24] Supplementary File 1 lists the 87 eligible psychological interventions and the 56 eligible CAM interventions.

**Literature Searches**

To identify relevant systematic reviews or meta-analyses, we searched MEDLINE® (via PubMed), EMBASE, the Cochrane Library, PsycINFO, and Epistemonikos. We used both index terms (e.g., Medical Subject Headings, Emtree) and free-text key words to search for MDD. We limited the electronic searches to "human," "English, German, or Italian language," "adults," and systematic reviews or meta-analyses. We searched sources from 1 January 2011 to 20 February 2017.

We imported all citations into an electronic database (EndNote X.6.0.1). The search strategies and yields of the searches appear in Supplementary File 2.

**Screening Process**

We developed and pilot-tested review forms using the eligibility criteria in Table 1. In a two-stage review process, two persons independently reviewed abstracts and full-text articles. We resolved discrepancies by consensus or by consulting a third, senior investigator. For each comparison and outcome we chose a single systematic review providing the best available evidence. If more than one systematic review on the same intervention met eligibility criteria, we chose the review with 1) the lowest risk of bias, 2) the most recent search date, and 3) the most

comprehensive scope. For each eligible systematic review, we determined whether RCTs included in it also met our inclusion criteria (see Table 1).

**Data Abstraction**

We designed and used a structured form to ensure consistency of data abstraction. If all studies in a systematic review met our eligibility criteria, we extracted summary estimates from meta-analyses. If one or more studies did not meet our eligibility criteria, we extracted data from individual studies. For example, when systematic reviews included mixed populations with different depressive disorders, we retrieved individual publications on patients with MDD. When data were unclear or contradictory, we contacted review authors for clarification. A second senior reviewer evaluated the completeness and accuracy of the data abstraction.

**Risk of Bias Assessment**

To assess methodological limitations (risk of bias) of eligible systematic reviews, we used the AMSTAR (Assessing Methodological quality of Systematic Reviews) tool.[25] Two independent reviewers assigned ratings for study limitations. They resolved any disagreements by consensus or by consulting a third, independent party. For the risk of bias of individual studies in a systematic review, we relied on the ratings of the original reviews' authors. We present AMSTAR ratings of included studies in Supplementary File 3.

**Evidence Synthesis**

Our aim was to depict the magnitude of beneficial and harmful treatment effects and the confidence that patients and clinicians can have in the underlying science about these effects. We used effect estimates of systematic reviews if all included RCTs met our eligibility criteria. In instances where individual RCTs of eligible systematic reviews did not meet our eligibility

criteria (e.g., because they used treatment as usual as a control group), we recalculated quantitative analyses removing ineligible studies.

For general efficacy, we were interested in the improvement of depressive symptoms. We present standardized mean differences because methods of assessments differed substantially across systematic reviews. A standardized mean difference of 0 indicates that both groups had similar improvements; effects of -0.5 or -1 indicate that 69 or 84 percent of patients in the intervention group, respectively, had greater reductions on depression scores than the average patient in the control group. For the risk of harms, we present overall discontinuation rates and discontinuation rates because of adverse events.

For the comparative efficacy of nonpharmacologic treatments with second-generation antidepressants, we used relative risks (RR) of response to treatment (as defined by the authors but most commonly presented as a 50% reduction of symptoms on a depression rating scale). If necessary, we recalculated RR so that a value below 1 would represent fewer responses of patients using nonpharmacologic treatments and a value greater than 1 more responses. We present treatment effects also as absolute risk reductions or increases (differences in numbers of patients who respond to treatment, per 1000 treated patients) with the related 95% confidence intervals.

**Quantitative Analyses**

As described above, in instances where individual RCTs of eligible systematic reviews did not meet our eligibility criteria, we recalculated quantitative analyses removing ineligible studies. To summarize data quantitatively, we followed established guidance.[26] For all analyses, we used both random- and fixed-effects models. We report results of random-effects analyses (DerSimonian & Laird). In general, the findings from the random- and fixed-effects analyses

were similar. We assessed statistical heterogeneity between studies by calculating the chi-squared statistic and Cochran's q. We used the $I^2$ statistic (the proportion of variation in study estimates attributable to heterogeneity) to estimate the magnitude of heterogeneity. We examined potential sources of heterogeneity using sensitivity analyses and assessed publication bias with funnel plots and Kendall's tests.

For general efficacy, we estimated standardized mean differences using Hedges' g.[27] If systematic reviews presented effect sizes as Cohen's d, we used a correction factor (J) to convert to Hedges' g: ($J = 1 - \frac{3}{4df-1}$), where df stands for "degrees of freedom".

If systematic reviews presented effect estimates of general efficacy as dichotomous outcomes, we calculated log odds ratios and converted them first to Cohen's d ($d =$ LogOddsRatio x $\frac{\sqrt{3}}{\pi}$) and then to Hedges' g using the correction factor presented above. For each estimate we calculated variances and confidence intervals.

For all statistical calculations we used Microsoft Excel (version 2010, Microsoft, Redmond, Washington, USA) or Review Manager 5.3 (Version 5.3. Copenhagen, The Cochrane Collaboration, 2014).

**Strength of the Evidence**

We graded the strength of evidence based on guidance for AHRQ Evidence-based Practice Centers on the use of GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group.[28, 29] Strength of evidence can take four grades: high, moderate, low, or insufficient. We considered grades of high or moderate strength as reliable evidence.

## RESULTS

Searches detected 2,532 citations; 19 systematic reviews met our eligibility criteria and provided the most recent summaries of evidence on 28 comparisons of interest.[30-44] Thirty-one additional systematic reviews formally met eligibility criteria, but their content was superseded by at least one of the 19 reviews mentioned above (Supplementary File 4). Figure 1 presents the flow of the literature; Table 2 presents characteristics of included reviews.

[Figure 1 about here]

For the majority of nonpharmacologic treatments, we did not find any systematically appraised evidence.

In the following sections, we first provide an overview of treatment effects of nonpharmacologic and common pharmacologic treatments compared with inactive interventions.

We then present results on the comparative benefits and harms of nonpharmacologic interventions and second-generation antidepressants.

**Table 2: Characteristics of included systematic reviews**

| Review | Risk of Bias | Years Covered by Searches | Eligible Study Designs | Population | Intervention | Control | K Relevant Studies, N Analyzed |
|---|---|---|---|---|---|---|---|
| Abbass 2014[40] | Low | NR to July 2012 | RCTs | Adults, ≥18 years of age, with common mental disorders, allowed comorbid medical or psychiatric disorders (relevant study of African American women, 20-50 years of age, with depression) | Psychodynamic therapies (short term) | Inactive treatment (waitlist) | Reduction: K=1, N=20 |
| Al-Karawi 2016[45] | Medium | NR to December 2015 | RCTs | Patients with nonseasonal depression diagnosed by standardized depression scales | Bright light therapy | Inactive treatment (placebo device and pill-placebo) | Reduction: K=1, N=62 |
| | | | | | | | Discontinuation (overall): K=1, N=62 |
| | | | | | | | Discontinuation (adverse events): K=1, N=62 |
| Apaydin 2016[46] | Medium | January 2007 to November 2014 | RCTs | Adults, ≥18 years of age, with a diagnosis of MDD | St. John's wort | Inactive treatment (pill-placebo) | Reduction: K=16, N=2888 |
| Appleton 2015[32] | Low | All years to May 2015 (except CINAHL, to September 2013) | RCTs, cross-over and cluster RCTs | Adults, ≥18 years of age, with a primary diagnosis of MDD or unipolar depressive disorder, allowed comorbid conditions | Omega-3 fatty acids (n-3PUFAs) | Inactive treatment (pill-placebo) | Reduction: K=6, N=308 |
| | | | | | | | Discontinuation (overall): K=7, N=446 |
| Cujipers 2014[41] | Medium | 1966 to January 2012 | RCTs | Adults diagnosed with a depressive disorder, allowed comorbid medical or psychiatric disorders | Humanistic therapy (Supportive therapy) | Inactive treatment (pill-placebo) | Reduction: K=1, N=101 |
| | | | | | Integrative therapy (Interpersonal therapy) | Inactive treatment (pill-placebo) | Reduction: K=1, N=33 |
| Ekers 2014[39] | High | 1966 to January 2013 | RCTs | Adults, ≥16 years of age, with a primary diagnosis of depression | Third Wave CBT (Behavioral activation therapy) | Inactive treatment (waitlist, placebo) | Reduction: K=9, N=338 |
| Furukawa | Medium | NR to | RCTs | Adults with MDD, | CBT | Inactive treatment | Reduction: K=5, N=509 |

| Review | Risk of Bias | Years Covered by Searches | Eligible Study Designs | Population | Intervention | Control | K Relevant Studies, N Analyzed |
|---|---|---|---|---|---|---|---|
| 2017[47] | | January 2015 | | diagnosed according to DSM or ICD-10 | | (pill-placebo) | |
| Galizia 2016[48] | Medium | NR to February 2016 | RCTs | Adults, aged 18 to 80 years with a diagnosis of major depression | SAMe | Inactive treatment (pill-placebo) | Reduction: K=2, N=142 |
| | | | | | | | Discontinuation (overall): K=2, N=142 |
| | | | | | | | Discontinuation (adverse events): K=1, N=124 |
| Gartlehner 2015[44] | Medium | January 1990 to September 2015 | RCTs, allowed nonrandomized studies for harms | Adults, ≥19 years of age, with MDD during initial treatment attempt or second treatment attempt among those who did not achieve remission after treatment with an SGA | Acupuncture | SGA | Response: K=93 (NWMA), N=173 |
| | | | | | CBT | SGA | Response: K=5 , N=660 |
| | | | | | Exercise | SGA | Response: K=90 (NWMA), N=0 |
| | | | | | Integrative therapy (Interpersonal psychotherapy) | SGA | Response: K=1, N=318 |
| | | | | | Omega-3 fatty acids | SGA | Response: K=92 (NWMA), N=40 |
| | | | | | SAMe | SGA | Response: K=90 (NWMA), N=0 |
| | | | | | St. John's wort | SGA | Response: K=9, N=1517 |
| | | | | | Third Wave CBT (Behavioral activation) | SGA | Response: K=2, N=243 |
| | | | | | SGA | Inactive treatment (pill-placebo) | Reduction: K=62, N=13759 |
| Josefsson 2014[36] | High | NR to April 2012 | RCTs | Adults, ≥18 years of age, with depression or depressive symptoms | Exercise (aerobic or nonaerobic exercise, as monotherapy or with usual care, excluding eastern meditative practices) | Inactive treatment (no treatment, placebo) | Reduction: K=11, N=368 |
| Jun 2014[31] | Medium | NR to February 2014 | RCTs, quasi-RCTs | Individuals of any age and either sex with depression, allowed comorbid diseases | Gan Mai Da Zao (decoction or modified decoction) | SGA | Response: K=3, N=148 |
| Linde | Medium | NR to | RCTs | Adults with | St. John's wort | Inactive treatment | |

| Review | Risk of Bias | Years Covered by Searches | Eligible Study Designs | Population | Intervention | Control | K Relevant Studies, N Analyzed |
|---|---|---|---|---|---|---|---|
| 2015[34] | | December 2013 | | prevalent or incident unipolar depressive disorder | | (pill-placebo) | Discontinuation (overall): K=4, N=619 |
| | | | | | | | Discontinuation (adverse events): K=3, N=522 |
| | | | | | TCA | Inactive treatment (pill-placebo) | Discontinuation (overall): K=4, N=484 |
| | | | | | | | Discontinuation (adverse events): K=3, N=421 |
| | | | | | SGA | Inactive treatment (pill-placebo) | Discontinuation (overall): K=5, N=1195 |
| | | | | | | | Discontinuation (adverse events): K=6, N=1572 |
| Liu 2015[37] | High | NR to February 2014 | RCTs | Older adults, mean age ≥60 years, with depressive symptoms, and allowed comorbidities | Tai Chi, Qigong | Inactive treatment (newspaper reading or reading and discussion group, health education) | Reduction: K=3, N=193 |
| Okumura, 2014[38] | High | 1994 to June 2013 | RCTs, cluster RCTs, quasi-RCTs | Adults, ≥18 years of age, with depression (elevated depressive symptoms, depressive disorders, or minor depression), allowed comorbid physical illness | CBT (group CBT, mindfulness-based cognitive therapy) | Inactive treatment (waitlist, pill-placebo) | |
| | | | | | | | Discontinuation (overall): K=7, N=834 |
| Sorbero 2015[33] | Medium | NR to January 2015 | RCTs | Adults, ≥18 years of age, with a clinical diagnosis of MDD at enrollment or formerly depressed if primary outcome of study was depression relapse or recurrence | Acupuncture (specific, needle or electroacupuncture) | Inactive treatment (nonspecific acupuncture) | Reduction: K=3, N=168 |

| Review | Risk of Bias | Years Covered by Searches | Eligible Study Designs | Population | Intervention | Control | K Relevant Studies, N Analyzed |
|---|---|---|---|---|---|---|---|
| Taylor 2014[43] | Medium | NR to March 2013 | RCTs | Adults with depression | Agomelatine | Inactive treatment (pill-placebo) | Reduction: K=12, N=3855 |
| Undurraga 2012[35] | High | 1980 to August 2011 | RCTs | Adults in an acute, apparently unipolar MDD episode or with ≤10% identified cases of bipolar depression or diagnoses other than MDD | TCA | Inactive treatment (pill-placebo) | Reduction: K=21, N=3094 |
| Van Marwijk 2012[42] | Low | All years to February 2012 | RCTs | Adults, ≥18 years of age, with a primary diagnosis of MDD, a depressive episode, or if considered depressed and eligible for antidepressant treatment by a clinician | Alprazolam | Inactive treatment (pill-placebo) | Reduction: K=5, N=603 |
| Yeung 2014[30] | Medium | NR to May 2013 | RCTs, quasi-RCTs | Individuals diagnosed with depression | Chinese herbal medicine | SGA | Response: K=5, N=1360 |
| | | | | | | Inactive treatment (pill-placebo) | Reduction: K=2, N=171 |
| | | | | | Saffron | SGA | Response: K=1, N=38 |
| | | | | | | Inactive treatment (pill-placebo) | Reduction: K=2, N=80 |
| | | | | | | | Discontinuation (overall): K=2, N=80 |

CBT = cognitive behavioral therapy. K = number of studies that were eligible for review of reviews. N = number of participants in eligible studies. n-3PUFAs = n-3 polyunsaturated fatty acids. MDD = major depressive disorder. NR = not reported. RCT = randomized control trial. SGA = second-generation antidepressant. TCA = tricyclic antidepressants.

**Nonpharmacologic and pharmacologic treatments compared with inactive interventions**

*Benefits of treatments*

Sixteen systematic reviews provided data on 17 comparisons with inactive interventions (placebo, sham interventions, or waiting list).[30-32, 35-37, 39-43, 45-50] Figure 2 provides an overview of treatment effects of nonpharmacologic and common pharmacologic treatments for MDD when compared with inactive interventions using standardized mean differences. The four commonly used pharmacologic interventions in the figure are agomelatine, alprazolam, second-generation antidepressants, and tricyclic antidepressants.

The comparisons in the figure are ordered by the strength of evidence grades and then alphabetically by the name of the intervention. Figure 2 also presents the numbers of trials and the total number of subjects in those trials; thus, the size of the circles reflects the numbers of participants (on a logarithmic scale). Supplementary File 5 provides detailed strength of evidence ratings.

[Figure 2 about here]

The only treatments for acute-phase MDD with high strength of evidence were second-generation antidepressants (Figure 2). Within this class, the medications rendered modest treatment effects (-0.35; 95% CI -0.31 to -0.38). Although the dataset included 24 unpublished studies,[44] treatment effects might still be inflated because several methods studies indicate that publication bias is a serious problem in this drug class.[51, 52]

Reviews on some psychological interventions (third wave cognitive behavioral therapy [CBT] and psychodynamic therapies) reported large treatment effects (third wave CBT: -0.97; 95% CI -0.6 to -1.34; psychodynamic therapies: -2.02; 95% CI -0.9 to -3.14; low, or insufficient strength of evidence, respectively; Figure 2). Studies of these two psychological interventions used waiting lists as control interventions. Patients on waiting lists usually do not experience

beneficial placebo effects, which can lead to artificially large treatment effects when active interventions are compared with waiting list controls. Placebo effects in psychiatric populations can be substantial; for example, on average 35 to 40% of patients in double-blinded trials of antidepressants achieved a response (usually defined as a 50% reduction of symptoms) to placebo treatment.[53]

For many of the therapies in Figure 2, the types of inactive comparators varied and involved different magnitudes of placebo effects. Consequently, comparisons of treatment effects across different interventions have to be made cautiously.

*Risk of harms*

Information on overall discontinuation and discontinuation because of adverse events was scarce. Figure 3 depicts the absolute risk reductions or increases for overall discontinuation and discontinuation because of adverse events – namely, the bars showing the 95% confidence intervals of either fewer or more discontinuations per 1000 patients. Only patients on second-generation antidepressants had a statistically significantly higher rate of discontinuation because of adverse events than patients on placebo (4.5% vs. 2.6%; RR 1.88, 95% CI 1.07 to 3.28). Most comparisons were of low or insufficient strength of evidence, indicating little certainty in the available effect estimates (details in Supplementary File 5).

[Figure 3 about here]

**Nonpharmacologic treatments compared with second-generation antidepressants**

Three systematic reviews provided data on response to treatment for 11 nonpharmacologic interventions (4 psychological, 6 CAM, and exercise) compared with second-generation antidepressants for the treatment of acute-phase MDD.[30, 31, 44] We used *response to treatment* as defined by authors of the reviews; in most cases, this was a 50% reduction of symptoms as

measured on a depression rating scale (e.g., Hamilton Depression Rating Scale). Figure 4 depicts the absolute risk reductions or increases for response to treatment per 1000 patients. As in the other figures, the comparisons are ordered by the strength of evidence grades and then alphabetically by the name of the intervention. These estimates are based on meta-analyses or, if meta-analyses were not feasible, on results from the largest and most reliable trial. Supplementary File 5 provides detailed information on our ratings of strength of evidence domains.

[Figure 4 about here]

*Psychological interventions*

One systematic review reported on the efficacy of four psychological treatments relative to second-generation antidepressants (Figure 4); these included CBT, integrative therapies, psychodynamic therapies, and third wave CBT.[44] The most reliable evidence (moderate strength of evidence) compared CBT with second-generation antidepressants. A meta-analysis of five RCTs of low or medium risk of bias with 660 patients provided consistent evidence that the two options had similar efficacy (45.5% versus 44.2%; RR, 1.10; 95% CI, 0.93 to 1.30).[54]. Including three high-risk-of -bias studies yielded similar results (RR, 0.98; 95% CI, 0.80 to 1.20).[54]

Integrative therapies also had response rates similar to those for antidepressants (low strength of evidence).[44] Patients treated with third wave CBT had significantly higher response rates than those on antidepressants, but the strength of evidence was insufficient because of the small sample size and under-dosing of antidepressants in the available trial. No evidence on response was available for psychodynamic therapies, but the available evidence indicated remission rates similar to those for second-generation antidepressants.[44]

*Complementary and alternative medicine interventions*

Three systematic reviews reported on comparisons with second-generation antidepressants for seven (of 56 eligible) CAM interventions – namely, acupuncture, Chinese herbal medicine (without Gan Mai Da Zao), Gan Mai Da Zao, omega-3-fatty acids, S-adenosyl-L-methionine (SAMe), St. John's wort, and saffron (Figure 4).[30, 31, 44] Except for omega-3-fatty acids, none of the comparisons yielded statistically significant differences. Based on results of a network meta-analysis, patients using omega-3-fatty acids were statistically significantly less likely to achieve response than patients on antidepressants (RR 0.51; 95% CI 0.33 to 0.79).[44] The reliability of results involving CAM interventions, however, is low. Therefore, the lack of statistical significance of most comparisons should not be interpreted as equivalence of treatment effects.

Some comparisons had wide confidence intervals (e.g., acupuncture, Gan Mai Da Zao, SAMe, saffron) rendering inconclusive findings about the comparative efficacy of treatments. Other comparisons had more precise results (e.g., Chinese herbal medicine or St. John's wort) but severe methodological shortcomings. For example, several trials of St. John's wort used moderate- or low-dose second-generation antidepressant regimens as comparators, not fully using the approved range of antidepressant doses.[44] Two of five trials comparing Chinese herbal medicine with antidepressants had serious design or analytic limitations such as flawed randomization or lack of allocation concealment.[30]

*Exercise*

A network meta-analysis produced inconclusive results about differences in response rates between physical exercise and second-generation antidepressants (Figure 4).[44]

*Comparative harms*

The discontinuation of treatment because of adverse events were generally lower for patients treated with nonpharmacological interventions than for those receiving second-generation antidepressants, although differences did not always reach statistical significance. Patients on St. John's wort had a statistically significantly lower rate of discontinuation because of adverse events (3.8% vs. 6.8%; RR 0.59; 95% CI 0.38 to 0.89).[44] Patients on any psychological treatment had a numerically lower risk for discontinuation of treatment because of adverse events (2.1% vs. 7.1%.; RR 0.37; 95% CI 0.12 to 1.12).[44] Likewise, patients who used physical exercise discontinued treatment because of adverse events less often than those treated with antidepressants (0%. vs. 6%; RR 0.15; 95% CI 0.01 to 2.86), but the difference did not reach statistical significance.[44] Little evidence on treatment discontinuation was available for most CAM interventions, particularly for Chinese herbal medicine or saffron.[30, 31]

## DISCUSSION

Out of more than 140 interventions of interest, our review identified only 5 treatments for which the general efficacy for acute-phase MDD is supported by reliable evidence (i.e., evidence graded as high or moderate strength of evidence). Among those, CBT is the only psychological and St. John's wort the only CAM intervention. For the vast majority of nonpharmacological interventions, either no systematic review evidence was available or the certainty of the evidence was severely limited. When compared with second-generation antidepressants, only CBT had similar efficacy based on moderate strength evidence. Overall, our analyses highlighted a lack of robust evidence for the majority of nonpharmacologic treatments.

To our knowledge, our study was the first review of systematic reviews assessing more than 140 interventions for treating adults with MDD. It provides a unique synthesis of the available, systematically appraised evidence on these treatment options, beyond the individual reviews on depression therapies that have been published over the past decade.

Our study does have several limitations, however. *First* and most importantly, like any review of systematic reviews, we could draw conclusions only about interventions that had been assessed by systematic reviews. Conceivably, RCTs are available for some interventions that have never been evaluated systematically in a review. Therefore, the absence of systematic reviews cannot be equated with an absence of RCTs. In addition, eligibility criteria of these reviews sometimes included only a subset of available studies (e.g., studies conducted in primary care settings). Such reviews do not provide a picture of the totality of the evidence but sometimes were the only ones that were available on a specific comparison of interest. *Second*, reviews of systematic reviews rely on results from other investigators. Although most of the reviews had few problems in methods, conceivably these authors did miss some RCTs. Likewise, we relied on the risk-of-bias appraisals of RCTs that authors of included systematic reviews had done. Most reviews used two independent reviewers to rate risk of bias; double checking their ratings was beyond the scope of our study. *Third*, reporting of characteristics of populations, interventions, comparators, and outcomes in included systematic reviews was often suboptimal. Frequently, we could not tell with certainty whether included populations were exclusively adult patients with acute-phase MDD; sometimes we could not determine the exact control interventions that authors had combined in their meta-analyses. We did not take several meta-analyses into consideration that combined studies with inactive treatments and treatment as usual as control interventions. Because treatment as usual cannot be viewed as "inactive," we believe

that such meta-analyses will lead to biased results. *Fourth*, as in any literature review, the reliability of our results is directly related to number of available studies and their quality. Some of the systematic reviews included only few studies with few events. The strength of evidence grades reflect these concerns and the certainty of our results; for most cases, these grades were low or insufficient. Such low strength of evidence indicates that future studies might have a substantial impact on the effect estimates reported in our review. Furthermore, we had no way to assess how meta-biases such as reporting biases or funding biases could have affected our findings. *Finally*, we did not take combination or augmentation strategies of antidepressants with nonpharmacologic interventions into consideration, but in clinical practice this is a common treatment strategy.

We believe that our results may have important clinical implications. They provide patients and clinicians with solid and up-to-date information about which treatment options have (or have not) been evaluated in rigorous systematic reviews. For patients with strong preferences against pharmacologic treatment, clinicians can offer therapies that have been compared directly with antidepressants. CBT, for example, is a well-supported, first-step alternative to pharmacologic treatment of MDD. Other psychologic or CAM interventions might be equally effective, or nearly so, but the evidence base is less reliable. The majority of psychologic and CAM interventions, however, are not evidence-based; given better alternatives, clinicians should probably advise against them. Such shared and informed decisionmaking might enhance treatment adherence[55] and could ultimately improve treatment outcomes for patients with MDD. This is especially important because treatment continuity is one of the main challenges in treating such patients.[56]

Our findings also highlight key areas of future research needs. Subsequent trials need to address gaps in our current knowledge about the efficacy of nonpharmacological interventions and about the comparative benefits and harms of pharmacologic and nonpharmacologic treatments for MDD. In particular, major research gaps pertain to information about the comparative risk of harms and patient-relevant outcomes such as functional capacity and quality of life. For patients and clinicians alike, balancing benefits and harms based on objective information is crucial. Lack of information about harms can lead to a biased knowledge base and the potential for decisions that cause more harm than good. Future studies should assess benefits and harms with standardized measures to allow for more direct comparisons across studies.

In the end, even in the absence of clearly informative evidence, clinicians and patients need to make decisions. They can discuss what is known and what is not known about the available options to treat MDD, and our work provides a way to start those conversations. For patients with strong preferences against pharmacologic treatments, clinicians should focus on therapies that have been compared directly with antidepressants. This review provides a framework to guide discussion of the potential options.

## DECLARATIONS

**Ethics approval:** Not required

**Consent for publication:** Not required

**Availability of data and materials:** The datasets used for meta-analyses are available from the corresponding author on reasonable request.

**Competing interests:** All authors declare that they have no competing interests.

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**Authors' contributions:** Gerald Gartlehner, Kathleen Lohr, and Meera Viswanathan developed the concept of the study; Gerald Gartlehner, Judith Greimel, Gernot Wagner, Nina Matyas, and Viktoria Titscher conducted the literature review; Gernot Wagner, Nina Matyas, and Viktoria Titscher abstracted data and conducted statistical analyses; Meera Viswanathan and Linda Lux rated the risk of bias of included systematic reviews; Gerald Gartlehner, Gernot Wagner, and Nina Matyas graded the strength of evidence; Bradley Gaynes provided clinical expertise throughout the study; Gerald Gartlehner and Kathleen Lohr wrote the first draft of the manuscript; all authors reviewed the manuscript and provided comments and revisions.

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# FIGURE LEGENDS

**Figure 1: Flow diagram of review of systematic reviews of treatments for major depressive disorder in adults**

**Figure 2: Overview of the strength of evidence of nonpharmacologic and pharmacologic interventions compared with inactive interventions for the treatment of adult major depressive disorder**

Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval; SAMe, S-adenosyl-L-methionine; SGA, second-generation antidepressants; SMD, standardized mean difference; TCA, tricyclic antidepressants

**Figure 3: Absolute risk reductions or increases of overall discontinuation or discontinuation because of adverse events comparing nonpharmacologic interventions with inactive interventions**

Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval; SAMe, S-adenosyl-L-methionine; SGA, second-generation antidepressants; TCA, tricyclic antidepressants

**Figure 4: Absolute risk reductions or increases of response to treatment comparing nonpharmacologic interventions with second-generation antidepressants for the treatment of adult major depressive disorder**

Abbreviations: CBT, cognitive behavioral therapy; ;CI, confidence interval; NWMA, network meta-analysis; RR, relative risk; SAMe, S-adenosyl-L-methionine; SGA, second-generation antidepressants.

[1] Number of participants in trials that directly compared intervention with second-generation antidepressants.

[2] Number of trials in network meta-analysis that contributed to the effect estimate

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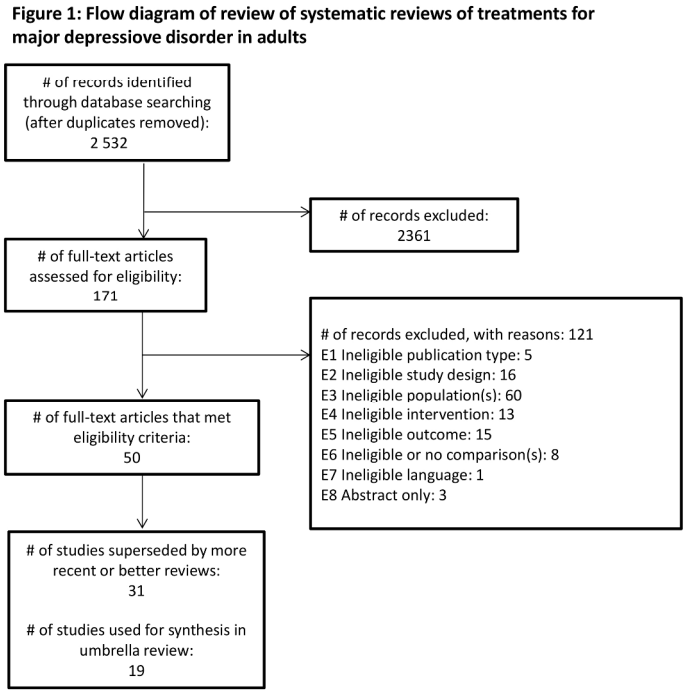


Figure 1: Flow diagram of review of systematic reviews of treatments for major depressiove disorder in adults

254x190mm (300 x 300 DPI)

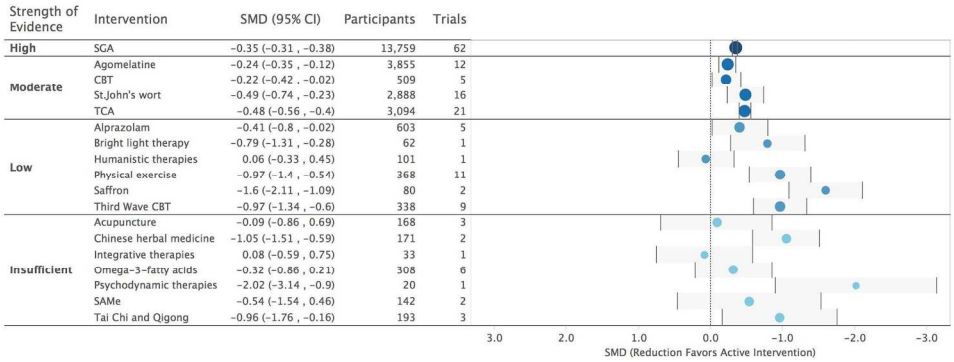


Figure 2: Overview of the strength of evidence of nonpharmacologic and pharmacologic interventions compared with inactive interventions for the treatment of adult major depressive disorder

169x62mm (300 x 300 DPI)

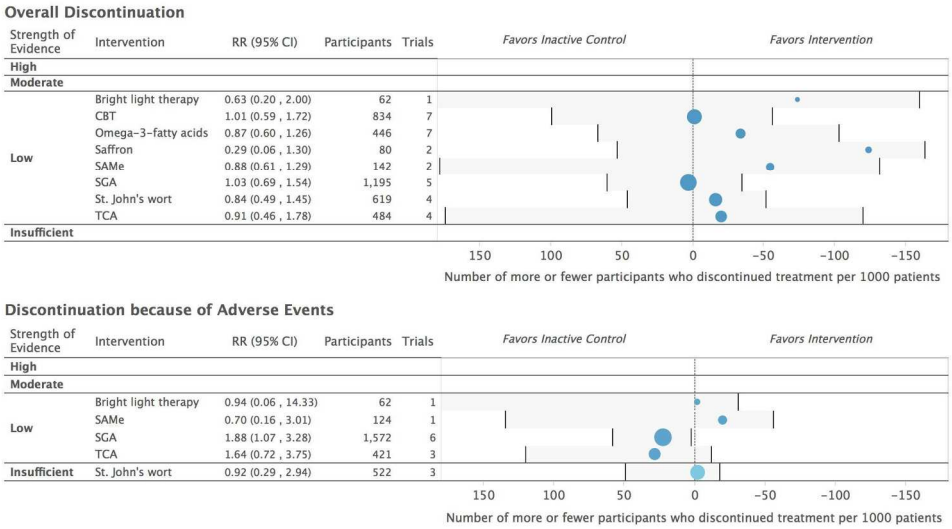


Figure 3: Absolute risk reductions or increases of overall discontinuation or discontinuation because of adverse events comparing nonpharmacologic interventions with inactive interventions

183x102mm (300 x 300 DPI)

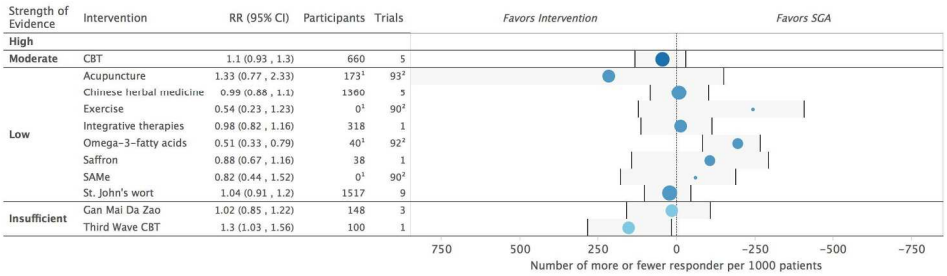


Figure 4: Absolute risk reductions or increases of response to treatment comparing nonpharmacologic interventions with second-generation antidepressants for the treatment of adult major depressive disorder

200x56mm (300 x 300 DPI)

**Supplementary File 1: Psychological and behavioral therapies**

| | |
|---|---|
| **Behavior Therapy / Behavior Modification**<br>• Activity Scheduling<br>• Assertiveness Training<br>• Aversion Therapy<br>• Behavior Contracting<br>• Behavior Modification<br>• Biofeedback, Psychology<br>• Contingency Management<br>• Conversion Therapy<br>• Distraction Therapy<br>• Exposure Therapy<br>• Pleasant Events<br>• Psychoeducation<br>• Problem-Focused<br>• Reciprocal Inhibition Therapy<br>• Relaxation Techniques<br>• Response Cost<br>• Sleep Phase Chronotherapy<br>• Social Skills Training | **Cognitive Behavioral Therapy**<br>• Problem Solving<br>• Rational Emotive Therapy<br>• Reality Therapy<br>• Restructuring<br>• Role Play<br>• Schemas<br>• Self-Control<br>• Stress Management |
| **Psychodynamic Therapies**<br>• Brief Psychotherapy<br>• Countertransference<br>• Freudian<br>• Group Therapy<br>• Insight Oriented Therapy<br>• Jungian<br>• Kleinian<br>• Object Relations<br>• Person Centered Therapy, Client-Centered Therapy<br>• Psychoanalytic Therapy<br>• Short-Term Psychotherapy<br>• Transference | **Third Wave Cognitive Behavioral Therapies**<br>• Acceptance And Commitment Therapy (ACT)<br>• Behavioral Activation<br>• Cognitive Behavioral Analysis System Of Psychotherapy (CBASP)<br>• Compassion-Focused<br>• Dialectical Behavior Therapy<br>• Diffusion<br>• Functional Analytic Psychotherapy (FAP)<br>• Metacognitive Therapy<br>• Mind Training<br>• Mindfulness |
| **Humanistic Therapies**<br>• Existential Therapy<br>• Experiential Therapy<br>• Expressive Therapy<br>• Griefwork<br>• Rogerian<br>• Non-Directive Therapy<br>• Supportive Therapy<br>• Transactional Analysis | **Integrative Therapies**<br>• Cognitive Analytical Therapy<br>• Counselling<br>• Eclectic Therapy<br>• Interpersonal Therapy<br>• Multimodal<br>• Transtheoretical |
| **Systemic Therapies**<br>• Conjoint Therapy<br>• Integrative Behavioral Couple Therapy (IBCT)<br>• Narrative Therapy<br>• Personal Construct<br>• Socioenvironmental Therapy<br>• Solution Focused Brief Therapy | **Other Psychologically-Oriented Interventions**<br>• Acting Out<br>• Age Regression Therapy<br>• Art Therapy<br>• Bibliotherapy<br>• Catharsis<br>• Colour Therapy<br>• Crisis Intervention<br>• Dance Therapy<br>• Drama Therapy<br>• Emotional Freedom Techniques<br>• Hypnotherapy<br>• Meditation [1]<br>• Morita Therapy<br>• Music Therapy<br>• Play Therapy<br>• Primal Therapy<br>• Psychodrama<br>• Reminiscence Therapy<br>• Sex Therapy |

Source: CCDAN[1]

**Supplementary File 1: Complementary and alternative medicine interventions**

| **Dietary Supplements** | **Other CAM Therapies** |
|---|---|
| • 5-hydroxy-L-tryptophan<br>• Carnitine/Acetyl-l-carnitine<br>• Chromium<br>• Folate<br>• Glutamine<br>• Inositol<br>• Magnesium<br>• Omega-3-fatty acids (fish oil)<br>• Phenylalanine<br>• SAMe (s-adenosylmethionine)<br>• Selenium<br>• Tyrosine<br>• Vitamin B6<br>• Vitamin B12<br>• Vitamin D<br>• Zinc | • Acupuncture<br>• Aromatherapy<br>• Autogenic training<br>• Ayurveda<br>• Bach Flower Remedies<br>• Bibliotherapy<br>• Craniosacral therapy<br>• Distraction<br>• Dolphins (swimming with)<br>• Homeopathyl<br>• Humor/humor therapy<br>• Hydrotherapy<br>• LeShan distance healing<br>• Massage<br>• Meditation<br>• Melatonin<br>• Music<br>• Nature-assisted therapy<br>• Negative air ionisation<br>• Painkillers<br>• Pets<br>• Prayer<br>• Qigong<br>• Recreational dancing<br>• Reiki<br>• Relaxation training<br>• Sleep deprivation<br>• Tai chi<br>• Yoga<br>• Young tissue extract |
| **Herbal Remedies** | |
| • Borage<br>• Ginkgo biloba<br>• Kampo<br>• Lavender<br>• Marijuana<br>• Rhodiola rosea (golden root)<br>• Saffron<br>• Schizandra<br>• St John´s wort<br>• Traditional Chinese herbal medicine | |

Source: beyondblue: A guide to what works for depression [http://resources.beyondblue.org.au/prism/file?token=BL/0556



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**Supplementary File 2: Search Strategies of Report, by Date**

**22 February 2016 / updated 20 February 2017**

PsycINFO (via EBSCOhost):

| Search | Query | Limiters/Expanders | Results |
|---|---|---|---|
| S1 | DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" | Search modes - Find all my search terms | 101,801 |
| S2 | TI ( (major OR mild OR moderate OR severe OR Chronic OR subsyndromal OR minor) N1 depress* ) OR AB ( (major OR mild OR moderate OR severe OR Chronic OR subsyndromal OR minor) N1 depress* ) | Search modes - Find all my search terms | 41,285 |
| S3 | TI ( Dysthymic N1 (Disorder OR depress*) ) OR AB ( Dysthymic N1 (Disorder OR depress*) ) | Search modes - Find all my search terms | 1,121 |
| S4 | TI Dysthymia OR AB Dysthymia | Search modes - Find all my search terms | 2,176 |
| S5 | S1 OR S2 OR S3 OR S4 | Search modes - Find all my search terms | 113,379 |
| S6 | (DE "Treatment Outcomes" OR DE "Psychotherapeutic Outcomes") OR (DE "Treatment Effectiveness Evaluation") OR (DE "Treatment") | Search modes - Find all my search terms | 112,193 |
| S7 | DE "Drug Therapy" | Search modes - Find all my search terms | 120,211 |
| S8 | DE "Antidepressant Drugs" OR (DE "Dietary Supplements") | Search modes - Find all my search terms | 18,225 |
| S9 | TI ( therap* OR psychotherap* OR antidepress* OR exercise* OR treat* ) OR AB ( therap* OR psychotherap* OR antidepress* OR treat* OR exercise*) OR SU ( therap* OR psychotherap* OR antidepress* OR exercise* ) | Search modes - Find all my search terms | 892,909 |
| S10 | S6 OR S7 OR S8 OR S9 | Search modes - Find all my search terms | 906,948 |
| S11 | S5 AND S10 | Search modes - Find all my search terms | 58,713 |
| S12 | S11 AND (TX adult*) | Search modes - Find all my search terms | 36,836 |
| S13 | (ZC "meta analysis") or (ZC "systematic review") | Search modes - Find all my search terms | 25,727 |
| S14 | TI ( meta analy* OR metaanaly* OR systematic review ) OR AB ( meta analy* OR metaanaly* OR systematic review ) | Search modes - Boolean/Phrase | 36,119 |
| S15 | S13 OR S14 | Search modes - Find all my search terms | 39,677 |
| S16 | S12 AND S15 | Search modes - Find all my search terms | 699 |
| S17 | S12 AND S15 | Limiters - Publication Year: 2011-2016 | 438 |

MEDLINE (via PubMed):

| Search | Query | Results |
|---|---|---|
| #1 | Search Depressive Disorder[Mesh:NoExp] | 63391 |
| #2 | Search Depressive Disorder, Major[Mesh] | 21464 |
| #3 | Search Dysthymic Disorder[Mesh] | 1038 |
| #4 | Search Depression[Mesh] | 166475 |
| #5 | Search major depress* [tiab] | 35468 |
| #6 | Search mild depress* [tiab] OR moderate depress* [tiab] OR severe depress* [tiab] | 5759 |
| #7 | Search Dysthymic Disorder [tiab] OR Dysthymic depress*[tiab] | 647 |
| #8 | Search Dysthymia [tiab] | 1927 |
| #9 | Search Chronic depression [tiab] | 753 |
| #10 | Search subsyndromal depress* [tiab] | 191 |
| #11 | Search minor depress* [tiab] | 1116 |
| #12 | Search #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 | 178291 |
| #13 | Search therapy[sh] | 5857380 |
| #14 | Search Treatment Outcome[mh] | 732516 |
| #15 | Search therapeutic use[sh] | 3706139 |
| #16 | Search drug therapy[sh] | 1814651 |
| #17 | Search Antidepressive Agents[Mesh] | 49765 |
| #18 | Search Psychotherapy[Mesh] | 164737 |
| #19 | Search Therapeutics[Mesh:NoExp] | 8140 |
| #20 | Search Complementary Therapies[Mesh] OR Phototherapy[Mesh] OR Magnetic Field Therapy[Mesh] OR Physical Therapy Modalities[Mesh] OR Combined Modality Therapy[Mesh] OR Dietary Supplements[Mesh] OR Drug Therapy[Mesh] | 1575104 |
| #21 | Search Exercise[Mesh] | 134612 |
| #22 | Search cam [sb] | 1017418 |
| #23 | Search therapy [tiab] OR therapies [tiab] | 1621447 |
| #24 | Search treat* [tiab] | 4211222 |
| #25 | Search antidepress* [tiab] | 53976 |
| #26 | Search #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 | 9792757 |
| #27 | Search (#12 AND #26) | 107642 |
| #28 | Search (#27 AND systematic[sb]) | 4376 |
| #29 | Search "Animals"[Mesh] NOT "Humans"[Mesh] | 4179330 |
| #30 | Search (#28 NOT #29) | 4373 |
| #31 | Search "Age Groups"[Mesh] NOT "Adult"[Mesh] | 1618187 |
| #32 | Search (#30 NOT #31) | 4074 |
| #33 | Search (#32) AND ("2011"[Date - Publication] : "3000"[Date - Publication]) | 1984 |
| #34 | Search (#33 AND (eng[la] OR ger[la] OR ita[la])) | 1936 |

Cochrane Library:

| Search | Query | Results |
|---|---|---|
| #1 | [mh ^"Depressive Disorder"] | 5022 |
| #2 | [mh "Depressive Disorder, Major"] | 2882 |
| #3 | [mh "Dysthymic Disorder"] | 146 |
| #4 | [mh Depression] | 6454 |
| #5 | ((major or mild or moderate or severe or chronic or subsyndromal or minor) next depress*):ti,ab,kw | 8376 |
| #6 | (dysthymic next (disorder or depress*)):ti,ab,kw | 251 |
| #7 | dysthymia:ti,ab,kw | 463 |
| #8 | depression:ti | 12767 |
| #9 | {or #1-#8} | 23563 |
| #10 | [mh /TH,TU,DT] | 286797 |
| #11 | [mh "Treatment Outcome"] | 111009 |
| #12 | [mh "Antidepressive Agents"] | 5363 |
| #13 | [mh psychotherapy] | 18569 |
| #14 | [mh therapeutics] | 267124 |
| #15 | [mh exercise] | 16764 |
| #16 | *therap*:ti,ab | 236773 |
| #17 | treat*:ti,ab | 410566 |
| #18 | antidepress*:ti,ab | 8050 |
| #19 | {or #10-#18} | 646531 |
| #20 | #9 and #19 | 19387 |
| #21 | #20 Publication Year from 2011 | 2265 |
| #22 | #21 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations | 688 |

EMBASE:

| No. | Query | Results |
|---|---|---|
| #1 | 'depressive disorder*':ab,ti OR depress*:ti | 155336 |
| #2 | 'major depression'/exp | 44356 |
| #3 | 'dysthymia'/exp | 6867 |
| #4 | (major NEAR/2 depress*):ab,ti | 46183 |
| #5 | ((mild OR moderate OR severe) NEAR/2 depress*):ab,ti | 11586 |
| #6 | (dysthymic NEAR/2 (disorder OR depress*)):ab,ti | 914 |
| #7 | dysthymia:ab,ti | 2465 |
| #8 | ((chronic OR subsyndromal OR minor) NEAR/2 depress*):ab,ti | 5010 |
| #9 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 | 185651 |
| #10 | 'therapy'/de OR 'acupuncture'/exp | 1290300 |
| #11 | 'treatment outcome'/exp | 1105591 |
| #12 | 'drug therapy'/de | 410725 |
| #13 | 'antidepressant agent'/exp | 345376 |
| #14 | 'psychotherapy'/exp | 206641 |
| #15 | 'meditation'/exp | 4793 |
| #16 | 'alternative medicine'/exp | 39082 |
| #17 | 'physical medicine'/exp | 471331 |
| #18 | 'natural products and their synthetic derivatives'/de OR 'omega 3 fatty acid'/exp OR 's adenosylmethionine'/exp OR 'hypericum perforatum extract'/exp | 34035 |
| #19 | 'hypericum perforatum'/exp | 2683 |
| #20 | 'exercise'/exp | 249136 |
| #21 | therapy:ab,ti OR therapies:ab,ti | 2076954 |
| #22 | treat*:ti | 1458457 |
| #23 | antidepress*:ab,ti | 74142 |
| #24 | #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 | 5575205 |
| #25 | #9 AND #24 | 82902 |
| #26 | [cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim | 174779 |
| #27 | 'systematic review':ab,ti | 83779 |
| #28 | 'meta analy*':ab,ti OR metaanaly*:ab,ti | 113691 |
| #29 | #26 OR #27 OR #28 | 223713 |
| #30 | #25 AND #29 | 3737 |
| #31 | #30 NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) | 3221 |
| #32 | 'animal'/exp NOT 'human'/exp | 4608503 |
| #33 | #31 NOT #32 | 3219 |
| #34 | 'groups by age'/exp NOT 'adult'/exp | 2250957 |
| #35 | #33 NOT #34 | 3110 |
| #36 | #35 AND [2011-2016]/py | 1399 |
| #37 | #36 AND ([english]/lim OR [german]/lim OR [italian]/lim) | 1353 |

Epistemonikos

| Query | Results |
|---|---|
| ((title:("major depress*" OR Dysthym* OR "subsyndromal depress*" OR "chronic depress*" OR "minor depress*") OR abstract:("major depress*" OR Dysthym* OR "subsyndromal depress*" OR "chronic depress*" OR "minor depress*")) OR title:depression) AND (title:(treat* OR therap* OR antidepress* OR psychotherap*) OR abstract:(therap* OR antidepress* OR psychotherap*)) NOT (child* OR adolesc*) | 4063 |
| Publication Type: Systematic Review | 911 |
| Publication Year: 2011 - 2016 | 433 |

Supplemental File 3: AMSTAR ratings of included studies

| Author, Year | RISK OF BIAS | Dual Screening and Extraction | Comprehensive literature search | Study quality assessed | 'A priori' design | Grey literature included | List of studies | Study characteristics provided | Scientific quality used appropriately | Appropriate methods to combine findings | Publication bias | Conflict of interest | Reason for High Risk of Bias Decision |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abbas, 2014 [1] | Low | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | - |
| Al-Karawi, 2016 [2] | Medium | Yes | Yes | Yes | Yes | NR | No | Yes | Yes | Yes | Yes | No | - |
| Apaydin, 2016 [3] | Medium | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | - |
| Appleton, 2015 [4] | Medium | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | - |
| Cuijpers, 2013 [5] | Medium | NR | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes | Yes | - |
| Ekers, 2014 [6] | High | No | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | No | No info on screening abstracts |
| Furukawa, 2017 [7] | Medium | NR | Yes | Yes | Yes | No | No | Yes | Yes | Yes | No | No | - |
| Galizia, 2016 [8] | Medium | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | - |
| Gartlehner , 2016 [9] | Medium | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | - |
| Josefsson, 2014 [10] | High | NR | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | No confirmation of dual screening or extraction |
| Jun, 2014 [11] | Medium | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | - |
| Linde, 2015 [12] | Medium | Yes | Yes | Yes | Yes | Yes | NR | Yes | No | Yes | Yes | Yes | - |
| Liu, 2014 [13] | High | No | Yes | Yes | Yes | NR | No | Yes | Yes | Yes | Yes | No | No information on screening methods or dual extraction |
| Okumura, 2014 [14] | High | No | Yes | yes | Yes | NR | No | Yes | Yes | Yes | No | No | No dual screening |
| Sorbero, 2015 [15] | Medium | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | - |
| Taylor, 2014 [16] | Medium | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | - |
| Undurraga, 2012 [17] | High | Yes | Yes | No | Yes | No | No | Yes | NA | Yes | No | No | No risk of bias assessment |
| van Marwijk, 2012 [18] | Low | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | - |
| Yeung, 2014 [19] | Medium | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | Yes | - |

NA = not applicable; NR = not reported

References

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**Supplementary File 4: Eligible reviews that were superseded by other reviews (k=31)**

| Superseded review | Intervention | Included review | Reason for decision |
|---|---|---|---|
| Amick et al., 2015[1] | CBT | Gartlehner et al., 2015[2] | Included systematic review was more comprehensive |
| Appleton et al 2016[3] | Omega-3-fatty acids | Appleton et al., 2015[4] | Included systematic review was more comprehensive |
| Chan et al. 2017[5] | Third Wave CBT | Ekers 2014[6] | Included systematic review was more comprehensive |
| Ciappolino et al. 2016[7] | Omega-3-fatty acids | Appleton et al., 2015[4] | Included systematic review considered more suitable |
| Cui et al. 2016[8] | St. John's wort | Gartlehner et al., 2015[2] | Included systematic review was more comprehensive |
| Cuijpers et al. 2016[9] | CBT | Okumura et al., 2014[10], Furukawa et al. 2017[11] | Included systematic reviews considered more suitable |
| Cuijpers et al. 2016[12] | CBT | Okumura et al., 2014[10], Furukawa et al. 2017[11] | Included systematic reviews considered more suitable |
| Cuijpers et al., 2011[13] | Integrative therapies | Cuijpers et al., 2014[14] | Included systematic review has a more recent search date |
| Cuijpers et al., 2012[15] | Humanistic therapies | Cuijpers et al., 2014[14] | Included systematic review has a more recent search date |
| de Souza Moura et al., 2015[16] | Exercise | Josefsson et al., 2014[17] | Included systematic review considered more suitable |
| Gartlehner et al., 2016[18] | Non-pharmacologic versus pharmacologic therapies | Gartlehner et al., 2015[2] | Included systematic review was more comprehensive |
| Grosso et al., 2014[19] | Omega-3-fatty acids | Appleton et al., 2015[4] | Included systematic review has a more recent search date |
| Hallahan et al. 2016[20] | Omega-3-fatty acids | Appleton et al., 2015[4] | Included systematic review was more comprehensive |
| Hausenblas et al., 2013[21] | Saffron | Yeung et al., 2014[22] | Included systematic review has a more recent search date |
| Hausenblas et al., 2015[23] | Saffron | Yeung et al., 2014[22] | Included systematic review considered more comprehensive |
| Johnsen et al., 2015[24] | CBT | Okumura et al., 2014[10], Furukawa et al. 2017[11] | Included systematic reviews considered more suitable |
| Kvam et al. 2016[25] | Exercise | Josefsson et al., 2014[17] | Included systematic review was more comprehensive |
| Kirkham et al., 2015[26] | Integrative therapies | Cuijpers et al., 2014[14] | Included systematic review considered more suitable |
| Ledochowski et al. 2016[27] | Exercise | Josefsson et al., 2014[17] | Included systematic review was more comprehensive |
| Linde et al., 2015[28] | CBT | Okumura et al., 2014[10], Furukawa et al. 2017[11] | Included systematic reviews considered more suitable |
| Linde et al., 2015[29] | CBT | Okumura et al., 2014[10], Furukawa et al. 2017[11] | Included systematic reviews considered more suitable |

| | | | |
|---|---|---|---|
| Maher et al. 2016[30] | St. John's wort | Apaydin 2016 et al. [31], Linde 2015[32] | Included systematic review was more comprehensive |
| Moore et al. 2016[33] | CBT | Okumura et al., 2014[10], Furukawa et al. 2017[11] | Included systematic reviews considered more suitable |
| Ng et al. 2017[34] | St. John's wort | Gartlehner et al., 2015[2] | Included systematic review was more comprehensive |
| Nystrom et al., 2015[35] | Exercise | Josefsson et al., 2014[17] | Included systematic review considered more suitable |
| Ren et al., 2015[36] | Chinese herbal medicine (class) | Yeung et al., 2014[22] | Included systematic review was more comprehensive |
| Schuch et al. 2016[37] | Exercise | Josefsson et al., 2014[17] | Included systematic review was more comprehensive |
| Weitz et al., 2015[38] | CBT | Gartlehner et al., 2015[2] | Included systematic review considered more suitable |
| Yang et al., 2015[39] | Omega-3-fatty acids | Appleton et al., 2015[4] | Included systematic review has a more recent search date |
| Yin et al., 2014[40] | Tai Chi and Qigong | Liu et al., 2015[41] | Included systematic review has a more recent search date |
| Zhang et al., 2014[42] | Shuganjieyu | Yeung et al., 2014[22] | Included systematic review was more comprehensive |

**CBT:** Cognitive behavioural therapy


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**Supplementary File 5: Summary of findings regarding response (nonpharmacologic interventions compared to second-generation antidepressants for the treatment of adult major depressive disorder).**

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **CBT compared to SGA for MDD**[1] | | | | | | | | | | | | |
| 5 | randomized trials | not serious | not serious | not serious | serious [1] | none | 142/312 (45.5%) | 154/348 (44.3%) | **RR 1.10** (0.93 to 1.30) | **44 more per 1.000** (from 31 fewer to 133 more) | ⊕⊕⊕◯ MODERATE | 1. Few events |
| **Acupuncture compared to SGA for MDD**[1] | | | | | | | | | | | | |
| 93 [1] | randomized trials | not serious | not serious | serious [2] | serious [3] | none | 46/73 (63.0%) | 65/100 (65.0%) | **RR 1.33** (0.77 to 2.33) | **215 more per 1.000** (from 150 fewer to 865 more) | ⊕⊕◯◯ LOW | 1. Based on network meta-analysis; 2 studies provided direct comparisons<br>2. Results are based on network meta-analysis<br>3. Few events not meeting optimal information size |
| **Chinese herbal medicine compared to SGA for MDD**[2] | | | | | | | | | | | | |
| 5 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 594/707 (84.0%) | 558/653 (85.5%) | **RR 0.99** (0.88 to 1.10) | **9 fewer per 1.000** (from 85 more to 103 fewer) | ⊕⊕◯◯ LOW | 1. 4 out of 5 studies are rated high risk of bias<br>2. Few events; study does not meet optimal information size |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **Exercise compared to SGA for MDD**[1] | | | | | | | | | | | | |
| 90 [1] | randomized trials | not serious | not serious | serious [2] | serious [3] | none | 31/100 (31.0%)[4] | 53/100 (53.0%)[4] | **RR 0.54** (0.23 to 1.23) | **244 fewer per 1,000** (from 122 more to 408 fewer) | ⨁⨁◯◯ LOW | 1. Based on network meta-analysis; No studies provided data for a direct comparison<br>2. Estimates are based on network meta-analysis.<br>3. Few events, confidence intervals cross threshold of appreciable difference.<br>4. No data from head-head studies available. Event rate is based on average events in placebo controlled trials |
| **Integrative therapies compared to SGA for MDD**[1] | | | | | | | | | | | | |
| 1 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 98/160 (61.3%) | 99/158 (62.7%) | **RR 0.98** (0.82 to 1.16) | **13 fewer per 1.000** (from 100 more to 113 fewer) | ⨁⨁◯◯ LOW | 1. High risk of bias due to insufficient reporting of methods and baseline differences between groups in duration of illness.<br>2. Sample size that does not fulfill optimal information size |
| **Omega-3 fatty acids compared to SGA for MDD**[1] | | | | | | | | | | | | |
| 92 [1] | randomized trials | serious [2] | not serious | serious [3] | not serious | none | 9/20 (45.0%) | 8/20 (40.0%) | **RR 0.51** (0.33 to 0.79) | **196 fewer per 1.000** (from 84 fewer to 268 fewer) | ⨁⨁◯◯ LOW | 1. Based on network meta-analysis; 2 studies provided direct comparisons<br>2. Suspected outcome reporting bias, only one of two studies reported response rates<br>3. Results are based on network meta-analysis |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **Saffron compared to SGA for MDD**[2] | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 15/19 (78.9%) | 17/19 (89.5%) | **RR 0.88** (0.67 to 1.16) | **107 fewer per 1.000** (from 143 more to 295 fewer) | ⊕⊕◯◯ LOW | 1. Few events; study does not meet optimal information size |
| **SAMe compared to SGA for MDD**[1] | | | | | | | | | | | | |
| 90 [1] | randomized trials | not serious | not serious | serious [2] | serious [3] | none | 36/100 (36.0%)[4] | 53/100 (53.0%)[4] | **RR 0.82** (0.44 to 1.52) | **95 fewer per 1.000** (from 276 more to 297 fewer) | ⊕⊕◯◯ LOW | 1. Based on network meta-analysis; 0 studies provided direct comparisons<br>2. Results are based on network meta-analysis<br>3. Small study size<br>4. No data from head-head trials available. Event rate is based on average events in placebo controlled trials |
| **St. John's wort compared to SGA for MDD**[1] | | | | | | | | | | | | |
| 9 | randomized trials | not serious | serious [1] | serious [2] | not serious | none | 419/770 (54.4%) | 386/747 (51.7%) | **RR 1.04** (0.91 to 1.20) | **21 more per 1.000** (from 47 fewer to 103 more) | ⊕⊕◯◯ LOW | 1. Moderate heterogeneity (I2=47%)<br>2. Most studies compared to low or moderate dose SGA |
| **Gan Mai Da Zao compared to SGA for MDD**[3] | | | | | | | | | | | | |
| 3 | randomized trials | serious [1] | not serious | not serious | very serious [2] | none | 56/76 (73.7%) | 52/72 (72.2%) | **RR 1.02** (0.85 to 1.22) | **14 more per 1.000** (from 108 fewer to 159 more) | ⊕◯◯◯ VERY LOW | 1. No blinding of study participants and personnel<br>2. Studies do not meet optimal information size |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **Third Wave CBT compared to SGA for MDD**[1] | | | | | | | | | | | | |
| 2 | randomized trial | very serious [1] | not serious | not serious | serious [2] | none | 66/93 (71.0%) | 76/150 (50.7%) | **RR 1.30** (1.03 to 1.56) | **152 more per 1.000** (from 15 more to 284 more) | ⊕◯◯◯ VERY LOW | 1. Dosage for one study capped below the upper limit of the typically prescribed range; suspected bias from one study's extremely high reported rates of response<br>2. Sample size does not fulfill optimal information size |

**CBT:** Cognitive behavioral therapy; **CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SGA:** Second generation antidepressant

**Supplementary File 5. Summary of findings regarding reduction in depression score (SMD) (nonpharmacologic and pharmacologic interventions compared to inactive interventions for the treatment of adult major depressive disorder).**

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **SGAs compared to inactive intervention for MDD**[1] | | | | | | | | | | | | |
| 62 | randomized trials | not serious | not serious | not serious | not serious | none | 8555 | 5204 | - | SMD **0.35 SD lower** (0.31 lower to 0.38 lower) | ⊕⊕⊕⊕ HIGH | |
| **Agomelatonin compared to inactive intervention for MDD**[4] | | | | | | | | | | | | |
| 12 | randomized trials | not serious | serious [1] | not serious | not serious | none | 2248 | 1607 | - | SMD **0.24 SD lower** (0.35 lower to 0.12 lower) | ⊕⊕⊕◯ MODERATE | 1. Some inconsistency, particularly between published and unpublished results; I-squared 66% |
| **CBT compared to inactive intervention for MDD**[5] | | | | | | | | | | | | |
| 5 | randomized trials | not serious | not serious | not serious | serious [1] | none | 509 (N total) | | - | SMD **0.22 SD lower** (0.42 lower to 0.02 lower) | ⊕⊕⊕◯ MODERATE | 1. Optimal information size not met |
| **St. John's wort compared to inactive intervention for MDD**[6] | | | | | | | | | | | | |
| 16 | randomized trials | not serious | serious [1] | not serious | not serious | none | 2888 (N total) | | - | SMD **0.49 SD lower** (0.74 lower to 0.23 lower) | ⊕⊕⊕◯ MODERATE | 1. I-squared 88.8% |
| **TCA compared to inactive intervention for MDD**[7] | | | | | | | | | | | | |
| 21 | randomized trials | not serious | not serious | not serious | not serious | publication bias strongly suspected [1] | 1577 | 1517 | - | SMD **0.48 SD lower** (0.56 lower to 0.4 lower) | ⊕⊕⊕◯ MODERATE | 1. Asymmetric funnel plot |
| **Alprazolam compared to inactive intervention for MDD**[8] | | | | | | | | | | | | |
| 5 | randomized trials | not serious | serious [1] | not serious | serious [2] | none | 305 | 298 | - | SMD **0.41 SD lower** (0.8 lower to 0.02 lower) | ⊕⊕◯◯ LOW | 1. I-squared 80%<br>2. Optimal information size not met |
| **Humanistic therapies compared to inactive intervention for MDD**[9] | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 51 | 50 | - | SMD **0.06 SD higher** (0.33 lower to 0.45 higher) | ⊕⊕◯◯ LOW | 1. Single study with 101 participants; does not meet optimal information size |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **Physical exercise compared to inactive intervention for MDD**[10] | | | | | | | | | | | | |
| 11 | randomized trials | serious [1] | serious [2] | not serious | not serious | none | 189 | 179 | - | SMD **0.97 SD lower** (1.4 lower to 0.54 lower) | ⊕⊕◯◯ LOW | 1. Most studies did not blind outcomes assessors and did not use ITT analyses<br>2. Some confidence intervals do not overlap; I-squared not reported |
| **Saffron compared to inactive intervention for MDD**[2] | | | | | | | | | | | | |
| 2 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 40 | 40 | - | SMD **1.6 SD lower** (2.11 lower to 1.09 lower) | ⊕⊕◯◯ LOW | 1. Small studies; do not reach optimal information size |
| **Third Wave CBT compared to inactive intervention for MDD**[11] | | | | | | | | | | | | |
| 9 | randomized trials | serious [1] | serious [2] | not serious | not serious | none | 170 | 168 | - | SMD **0.97 SD lower** (1.34 lower to 0.6 lower) | ⊕⊕◯◯ LOW | 1. Most trials have limitations regarding methods of randomization and blinding of outcomes assessors<br>2. Some confidence intervals do not overlap |
| **Acupuncture compared to inactive intervention for MDD**[12] | | | | | | | | | | | | |
| 3 | randomized trials | serious [1] | serious [2] | not serious | very serious [3] | none | 86 | 82 | - | SMD **0.09 SD lower** (0.86 lower to 0.69 higher) | ⊕◯◯◯ VERY LOW | 1. One of the studies did not use ITT<br>2. I-squared high; some confidence intervals hardly overlap<br>3. Does not reach optimal information size |
| **Chinese herbal medicine compared to inactive intervention for MDD**[2] | | | | | | | | | | | | |
| 2 | randomized trials | very serious [1] | not serious | serious [2] | serious [3] | none | 113 | 58 | - | SMD **1.05 SD lower** (1.51 lower to 0.59 lower) | ⊕◯◯◯ VERY LOW | 1. High risk of bias in 1 out of 2 studies<br>2. Unclear how applicable studies are to Western populations<br>3. Does not fulfill optimal information size |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **Integrative therapy compared to inactive intervention for MDD**[9] | | | | | | | | | | | | |
| 1 | randomized trials | serious [1] | not serious | not serious | very serious [2] | none | 19 | 14 | - | SMD **0.08 SD higher** (0.59 lower to 0.75 higher) | ⊕◯◯◯ VERY LOW | 1. Inadequate randomization and allocation concealment<br>2. Very few participants; does not meet optimal information size |
| **Omega-3 fatty acids compared to inactive intervention for MDD**[13] | | | | | | | | | | | | |
| 6 | randomized trials | serious [1] | serious [2] | not serious | serious [3] | none | 182 | 126 | - | SMD **0.32 SD lower** (0.86 lower to 0.21 higher) | ⊕◯◯◯ VERY LOW | 1. Some studies do not provide ITT results and strongly favor intervention; in most studies it is unclear how the taste of omega-3 fatty acids were masked<br>2. I-squared 77%; Some confidence intervals do not overlap<br>3. Confidence interval crosses clinically relevant benefits or harms |
| **Psychodynamic therapies compared to inactive intervention for MDD**[14] | | | | | | | | | | | | |
| 1 | randomized trials | serious [1] | not serious | not serious | very serious [2] | none | 10 | 10 | - | SMD **2.02 SD lower** (3.14 lower to 0.9 lower) | ⊕◯◯◯ VERY LOW | 1. Small study with unclear randomization and allocation concealment<br>2. Very small study; does not reach optimal information size |
| **Tai Chi and Qigong compared to inactive intervention for MDD**[15] | | | | | | | | | | | | |
| 3 | randomized trials | serious [1] | serious [2] | not serious | serious [3] | none | 91 | 102 | - | SMD **0.96 SD lower** (1.76 lower to 0.16 lower) | ⊕◯◯◯ VERY LOW | 1. Outcomes assessors not blinded in all trials<br>2. High I-squared; some confidence intervals not overlapping<br>3. Does not reach optimal information size |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **SAMe compared to inactive intervention for MDD[16]** | | | | | | | | | | | | |
| 2 | randomized trials | not serious | Serious [1] | not serious | very serious [2] | none | 74 | 68 | - | SMD 0.54 **SD lower** (1.54 lower to 0.46 higher) | ⊕◯◯◯ VERY LOW | 1. High I-squared<br>2. Does not reach optimal information size |
| **Bright light therapy compared to inactive intervention for MDD[17]** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | not serious | very serious [1] | | 32 | 30 | - | SMD **0.79 SD lower** (1.31 lower to 0.28 lower) | ⊕⊕◯◯ LOW | 1. Does not reach optimal information size |

**CBT:** Cognitive behavioral therapy; **CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SAMe:** S-adenosyl methionine; **SGA:** Second generation antidepressant; **SMD:** Standardized mean difference

**Supplementary File 5. Summary of findings regarding overall discontinuation (nonpharmacologic interventions compared to inactive interventions for the treatment of adult major depressive disorder).**

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **CBT compared to inactive intervention for MDD**[18] | | | | | | | | | | | | |
| 7 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 51/398 (12.8%) | 60/436 (13.8%) | **RR 1.01** (0.59 to 1.72) | **1 more per 1.000** (from 56 fewer to 99 more) | ⊕⊕◯◯ LOW | 1. Outcomes assessors often not blinded<br>2. Few events; confidence intervals cross clinically relevant benefits or harms |
| **Omega-3 fatty acids compared to inactive intervention for MDD**[13] | | | | | | | | | | | | |
| 7 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 61/272 (22.4%) | 45/174 (25.9%) | **RR 0.87** (0.60 to 1.26) | **34 fewer per 1.000** (from 67 more to 103 fewer) | ⊕⊕◯◯ LOW | 1. Some studies do not provide ITT results and strongly favor intervention; in most studies it is unclear how the taste of omega-3 fatty acids were masked<br>2. Confidence interval crosses clinically relevant benefits or harms |
| **Saffron compared to inactive intervention for MDD**[2] | | | | | | | | | | | | |
| 2 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 2/40 (5.0%) | 7/40 (17.5%) | **RR 0.29** (0.06 to 1.30) | **124 fewer per 1.000** (from 53 more to 164 fewer) | ⊕⊕◯◯ LOW | 1. Few events; study does not reach optimal information size |
| **SGAs compared to inactive intervention for MDD**[19] | | | | | | | | | | | | |
| 5 | randomized trials | not serious | not serious | not serious | serious [1] | publication bias strongly suspected [2] | 70/674 (10.4%) | 58/521 (11.1%) | **RR 1.03** (0.69 to 1.54) | **3 more per 1.000** (from 35 fewer to 60 more) | ⊕⊕◯◯ LOW | 1. Few events; does not meet optimal information size<br>2. Not all trials report overall discontinuation |
| **St. John's wort compared to inactive intervention for MDD**[19] | | | | | | | | | | | | |
| 4 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 26/334 (7.8%) | 29/285 (10.2%) | **RR 0.84** (0.49 to 1.45) | **16 fewer per 1.000** (from 46 more to 52 fewer) | ⊕⊕◯◯ LOW | 1. Very few events; optimal information size not reached |
| **TCA compared to inactive intervention for MDD**[19] | | | | | | | | | | | | |

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| 4 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 50/246 (20.3%) | 53/238 (22.3%) | **RR 0.91** (0.46 to 1.78) | **20 fewer per 1.000** (from 120 fewer to 174 more) | ⊕⊕◯◯ LOW | 1. 3 out of 4 studies have serious limitations<br>2. Few events; does not meet optimal information size |
| **SAMe compared to inactive intervention for MDD[16]** | | | | | | | | | | | | |
| 2 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 29/74 (39.2%) | 31/68 (45.6%) | **RR 0.88** (0.61 to 1.29) | **55 fewer per 1.000** (from 132 more to 178 fewer) | ⊕⊕◯◯ LOW | 1. Very few events |
| **Bright light therapy compared to inactive intervention for MDD[17]** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 4/32 (12.5%) | 6/30 (20.0%) | **RR 0.63** (0.20 to 2.00) | **74 fewer per 1.000** (from 160 fewer to 200 more) | ⊕⊕◯◯ LOW | 1. Very few events |

**CBT:** Cognitive behavioral therapy; **CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SAMe:** S-adenosyl methionine**; SGA:** Second generation antidepressant

**Supplementary File 5. Summary of findings regarding discontinuation due to adverse events (nonpharmacologic interventions compared to inactive interventions for the treatment of adult major depressive disorder).**

| Quality assessment | | | | | | | № of patients | | Effect | | Strength of evidence | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Control | Relative (95% CI) | Absolute (95% CI) | | |
| **SGAs compared to inactive intervention for MDD**[19] | | | | | | | | | | | | |
| 6 | randomized trials | not serious | not serious | not serious | serious [1] | publication bias strongly suspected [2] | 41/865 (4.7%) | 18/707 (2.5%) | **RR 1.88** (1.07 to 3.28) | **22 more per 1.000** (from 2 more to 58 more) | ⊕⊕◯◯ LOW | 1. Few events; does not meet optimal information size<br>2. Not all trials report discontinuation because of adverse events |
| **St. John's wort compared to inactive intervention for MDD**[19] | | | | | | | | | | | | |
| 3 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 6/286 (2.1%) | 6/236 (2.5%) | **RR 0.92** (0.29 to 2.94) | **2 fewer per 1.000** (from 18 fewer to 49 more) | ⊕⊕◯◯ LOW | 1. Very few events; optimal information size not reached |
| **TCA compared to inactive intervention for MDD**[19] | | | | | | | | | | | | |
| 3 | randomized trials | serious [1] | not serious | not serious | serious [2] | none | 15/214 (7.0%) | 9/207 (4.3%) | **RR 1.64** (0.72 to 3.75) | **28 more per 1.000** (from 12 fewer to 120 more) | ⊕⊕◯◯ LOW | 1. 2 out of 3 studies have serious limitations<br>2. Few events; does not meet optimal information size |
| **SAMe compared to inactive intervention for MDD**[16] | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 3/64 (4.7%) | 4/60 (6.7%) | **RR 0.70** (0.16 to 3.01) | **20 fewer per 1.000** (from 56 fewer to 134 more) | ⊕⊕◯◯ LOW | 1. Very few events |
| **Bright light therapy compared to inactive intervention for MDD**[17] | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | not serious | very serious [1] | none | 1/32 (3.1%) | 1/30 (3.3%) | **RR 0.94** (0.06 to 14.33) | **2 fewer per 1.000** (from 31 fewer to 444 more) | ⊕⊕◯◯ LOW | 1. Very few events |

**CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SAMe:** S-adenosyl methionine; **SGA:** Second generation antidepressant

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# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6-7 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supp File 2 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7-8 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 8 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8, Table 1 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 9 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 9-10 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 10 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 10 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 10, Figure 1, Supp File 3 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 11, Table 2 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 11, Supp File 4 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 12, Figures 2 - 5, Supp File 5 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 12-16 Figure 3 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 16-17 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 17 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 17-18 |
| **FUNDING** | | | |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 19 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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